BRAIN

A JOURNAL OF NEUROLOGY

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A Journal of Neurology

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MACMILLAN & CO., LIMITED
ST. MARTIN'S STREET, LONDON
NEW YORK: THE MACMILLAN COMPANY
1952

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March, 1952

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VOL. 75, PART 1.

THE RACEMOSE FORM OF CEREBRAL CYSTICERCOSIS

BY

EDWIN R. BICKERSTAFF, P. C. P. CLOAKE, BRODIE HUGHES AND W. T. SMITH

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Cysticercosis cerebri can no longer be regarded as a curiosity in this country, though described as "excessively rare" by Broughton-Alcock and others in 1928. The first definite records of the condition in England are those of Ottley and Forbes (1843) and Brittan (1859), for in the earlier report by Dagleish (1832) the cyst was probably a hydatid. The investigation of soldiers returning from overseas service, at the Millbank Military Hospital, enabled MacArthur (1934) and Dixon and Smithers (1934) to report on a large series of cases, and by combining their own with other cases from the literature, 284 cases were reviewed by Dixon and Hargreaves (1944) and the importance of the condition as a cause of epilepsy in patients who had lived in the East was fully confirmed.

The diagnoses had been made (*a*) directly—by craniotomy or autopsy; (*b*) radiographically—by demonstration of intracerebral calcification, or (*c*) presumptively—by demonstration of calcified cysts in muscles or by biopsy of subcutaneous nodules, while supporting evidence was often obtained from eosinophilia in blood or cerebrospinal fluid.

These features are not invariably present, however, nor does cysticercosis invariably manifest itself as a series of discrete cysts. From the literature, the racemose form appears to have been overlooked in this country, and no clear record of its occurrence has been found. It is, however, no new discovery. Zenker (1882) gave the name *Cysticercus racemosus* to the lesions found at the base of the brain occasionally termed *C. botryoides* or *C. multilocularis*. Fantham *et al.* (1916) wrote: "At the base of the brain the cysticerci *as a rule* assume that form which is designated as *C. racemosus*, and consists of rows of delicate grape-like bladders in groups, sometimes also markedly branched, but generally sterile, which develop in the meshes of the soft meninges and may envelop the nerves and vessels of the base of the brain." Kinnier Wilson (1940) drew attention to the formation of racemose clusters around the

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base of the brain, while in other countries this form is not only well recognized but considered common. Dandy (1932) remarked that cysticerci were *especially* liable to form racemose clusters in the basal cisterns. Dolgopol and Neustaedter (1935), describing such a case, say ". . . in the latter case (at the base of the brain) the cysticercus often assumes a racemose (grape-like) appearance" and they quote Vosgien (1911) as saying that this variety is seen in one-sixth of all cases of cysticercosis of the brain. Arana and Asenjo (1945) describe 20 cases of cerebral cysticercosis in 13 of which the racemose form was found either at operation or autopsy, and say "Usually supratentorial cysticercosis is intraparenchymal (encysted). This is not true of cysticercosis of the posterior fossa cisternæ, where racemose clusters ('bunches of grapes') are found." There are numerous other reports in continental and South American journals, from which one further quotation will be taken—"the commonest form of basilar cysticercosis in older subjects usually follows a slower course and anatomically the cysts correspond to the so-called cysticercosis racemosa" (Obrador, 1948).

The case which we have studied is being reported in detail not only to draw attention to the importance of this variety of cysticercosis but also to illustrate how such a lesion is capable of giving a clinical picture differing considerably from that usually considered in this country typical of the disease.

Case Report

M. H., female. Admitted to the Neurological Unit at the Queen Elizabeth Hospital, Birmingham, on July 31, 1950, aged 50.

There was no relevant family history and her early life had been uneventful.

In 1923, aged 23, she went to live in India, and within twelve months of arrival, while pregnant, had an attack of severe headache culminating in loss of consciousness for twenty-four hours. A similar attack occurred, again during pregnancy, eight years later, and following this she suffered recurrent headaches, but no more serious disorder, until 1943, when she had returned to England.

In April 1943 (aged 43) she had a generalized epileptic fit. For the next two months she suffered repeated attacks of occipital headache and vomiting, the last of which continued for nine days during which she became increasingly drowsy and disorientated, and on June 2, 1943, was admitted to Dudley Road Hospital, Birmingham.

She was drowsy and disorientated, and apparently suffering severe headache, with vomiting three or four times a day. There was nystagmus on lateral gaze but no other abnormal signs in the nervous system. X-ray of skull and chest were normal. A blood-count showed a hæmoglobin of 78 per cent. The cerebrospinal fluid pressure was 160 mm., and the Queckenstedt normal. The fluid contained 180 white cells, "mainly lymphocytes," and 55 mg. per cent of protein. The Lange curve read 1123211000.

For two weeks she remained in this condition, and then rapidly improved, refused further investigation, and discharged herself on June 30, 1943.

Six months later she had a further severe headache followed by several hours of unconsciousness. She was admitted to the Queen Elizabeth Hospital, Birmingham, on December 7, 1943. By the time of her admission she had recovered consciousness, but was mentally confused and showed slight weakness of the left hand which recovered during the next few days. There were no other abnormal physical signs.

X-ray of skull and chest were normal. A full blood-count showed R.B.C. 5,380,000; Hb 62 per cent; C.I. 0·57. W.B.C. 7,400, polymorphs. 46 per cent, eosinophils 3 per cent (= 222/c.mm.). Cerebrospinal fluid pressure was 140 mm. and the Queckenstedt normal. The fluid contained 270 cells (90 per cent mononuclear) and a protein of 150 mg. per cent. Sugar and chlorides were normal. The Lange curve now read 5433221000. The Wassermann reaction was negative in blood and C.S.F.

She again recovered spontaneously and discharged herself before investigations were completed so that a tentative diagnosis of "encephalitis" was all that it was possible to make.

For the next two years she suffered recurrent severe headaches, with one further attack of vomiting and mental confusion. She showed slight general mental deterioration and became unsteady in gait, but refused all offers of further investigation.

In 1946 (aged 46) her unsteadiness increased and her vision became blurred and following three further attacks of headache, vomiting, and loss of consciousness she was readmitted to the Neurological Unit at the Queen Elizabeth Hospital, Birmingham, on September 27, 1946.

She was conscious but disorientated, unco-operative, and at times noisy. It is recorded that she was constantly restless. The abnormal signs in the central nervous system had now increased. There was bilateral papillœdema, and skew deviation of the eyes. The left arm was weak, and there was ataxia of the left arm and leg. Tendon reflexes were exaggerated bilaterally, and the abdominal reflexes were absent. The plantar reflexes were flexor. X-ray of chest, skull and abdomen were normal. Blood sugar, gastric contents and fæces were normal. The red blood-count was now normal and of 8,950 white cells/c.mm., 58 per cent were polymorphs and 5 per cent eosinophils (= 300 per c.mm.). The cerebrospinal fluid pressure was 240 mm. but the cytology was now normal. The protein was 74 mg. per cent and the remainder of the biochemical analysis normal, as was the Lange curve.

The electroencephalogram showed diffuse, gross abnormality without any indication of a focus. Frequent long bursts of high amplitude delta waves occurred synchronously in all leads, together with persistent low amplitude theta rhythms. The abnormality was equally distributed on the two sides and in all areas. A very poorly developed unstable alpha rhythm was seen intermittently in the occipital leads. Ventriculography was not carried out because the patient refused further investigation and discharged herself.

Between 1946 and 1950 she was increasingly incapacitated by headaches, and her gait became so unsteady that she was able to walk only with assistance. In addition she developed a series of "fits" in which, following a sensation of giddiness, all four limbs would become rigidly extended. She would then lose consciousness for about fifteen minutes during which time she was incontinent. There were no clonic movements. The restlessness which had been noted in hospital in 1946, and which her relatives had noted for eight years, gradually increased until it was evident that she was suffering from widespread involuntary movements affecting all parts of the body, which by June 1950 had become so severe that she was unable to feed herself or perform her toilet.

She was readmitted to the Neurological Unit at the Queen Elizabeth Hospital, Birmingham, on July 31, 1950, now aged 50. She was conscious and alert but showed gross deterioration of mental capacities, very poor powers of memory, and complete inability to carry out the more complex instructions or to do the simplest arithmetic. Her concentration was very poor and she was markedly euphoric.

The most striking feature of the examination was the gross involuntary movements which were greatly exaggerated by exertion or emotion. They were continuously present, choreiform in type, and often of very great amplitude. Even during sleep, fragmentary movements of the limbs occurred. All parts of the body were affected and the movements were accompanied by a loud grunting tic.

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Examination was considerably impeded by these movements. The eyes showed bilateral papillœdema thought to be of long-standing. Visual acuity was less than 6/60 in both eyes. The fields could not adequately be tested. Pupils reacted sluggishly to light, but normally on accommodation. The remainder of the cranial nerves were normal. There was bilateral hypotonia of the arms, and a generalized weakness of the left arm. There was a mild ataxia, largely masked by the involuntary movements. Sensation was normal. The tendon reflexes showed bilateral exaggeration. Abdominal reflexes were absent. The legs showed bilateral hypotonia and generalized slight weakness of the left leg. There was a mild bilateral ataxia. The reflexes were all equally exaggerated but the plantar reflexes were flexor. Sensation was normal. The gait showed a severe disturbance of equilibration, out of all proportion to the ataxia demonstrated with the patient recumbent, and making walking impossible without assistance.

Results of investigations were as follows: Red blood-count 4,590,000; Hb 82 per cent; C.I. 0·89. White blood-count 8,500. Polymorphonuclear cells 55 per cent, eosinophils 11 per cent (= 935/c.mm.), lymphocytes 31 per cent, monocytes 2 per cent. Wassermann reaction negative.

X-ray of the chest was normal. X-ray of the skull now showed erosion of the posterior clinoid processes, but no intracranial calcification.

A ventriculography was carried out and showed gross bilateral dilatation of the ventricles with enlargement of the third ventricle and enormous distension of the fourth ventricle. The right temporal horn appeared to be displaced medially. No air had escaped from the fourth ventricle (*see* figs. 1 and 2). The composition of the ventricular fluid was normal.

It appeared from the ventriculography that there were two lesions present, the one in the right temporal lobe and the other in the posterior fossa causing obstruction to the roof foramina in the fourth ventricle. In view of the patient's deterioration,

FIG. 1.—Ventriculogram, lateral view, showing gross distension of ventricular system.

FIG. 2.—Ventriculogram. Reverse Towne's view, showing hydrocephalus and apparent medial displacement of right temporal horn.

and bearing in mind the severe disturbance of equilibration, it was decided to explore the posterior fossa first, and this was carried out by one of us (B. H.) on August 31, 1950.

Posterior Fossa Exploration (B. H.)

The central area of the posterior fossa and upper cervical cord was exposed through a mid-line incision. A generous bone removal was undertaken to effect this exposure, including the arch of the atlas.

Findings.—Over the whole of the area exposed the arachnoid was thickened and milky, and in both lateral recesses the arachnoidal thickening was so dense as to obscure the lower cranial nerves from view. Overlying the lower end of the fourth ventricle, probably in the cisterna magna, there was a fibrous mass, looking exactly like a piece of fascia rolled up. To this were attached bunches of grape-like cysts, about 0·5 cm. diameter, and filled with clear fluid. The whole mass was apparently quite free of arachnoidal attachment, and on lifting it out of the cisterna magna further clusters of cysts appeared which had been lying on the posterior aspect of the upper cervical cord. The roof foramina of the fourth ventricle could not be identified, and although the fourth ventricle appeared to be greatly dilated on ventriculography films, no entry into it was effected.

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The surgical manipulations in the region of the medulla had affected the patient's blood pressure and pulse adversely, and as it was felt that surgical procedures would have little value in the face of such extensive arachnoidal disease, the operation was terminated at this point and the wound closed in the usual layers.

Post-operative course.—The patient lived for three weeks following the craniotomy, but remained in a semi-stuporose condition. She was rousable and would answer simple questions, but showed great apathy, and was incontinent of urine and fæces. She had no voluntary movement of the arms, and the involuntary movements in these had ceased entirely. The legs, however, made continuous involuntary rhythmical movements of flexion and extension. She developed a bronchopneumonia and died on September 21, 1950.

Pathological Examination (W. T. S.)

Surgical specimen.—This was a racemose cystic structure, composed of several major projections, each of which arose from a common pedicle and measured approximately 6 cm. in length. These major projections consisted of elongated clusters of cystic buds, but elaborate digitate ramifications at the tips of the buds were not seen. Two of these projections were detached immediately after the surgical exploration and examined microscopically as wet preparations; parasitic structures were not seen. This precursory examination was carried out for diagnostic purposes before photography of the gross specimen (fig. 3), which therefore does not depict the full extent of the lesion. The cyst wall was fragile, almost transparent, smooth and free from nodules. In the region of the pedicle

FIG. 3.—Racemose structure removed from the posterior fossa. Two clusters of cysts were detached for examination prior to photography. (× 1·7).

it was thicker, tougher and greyish-white in colour. Colourless fluid was collected from the cyst after operation and centrifuged, but no scolices or hooklets were seen on microscopy of the deposit.

Microscopically the cyst wall consists of three layers (fig. 4):

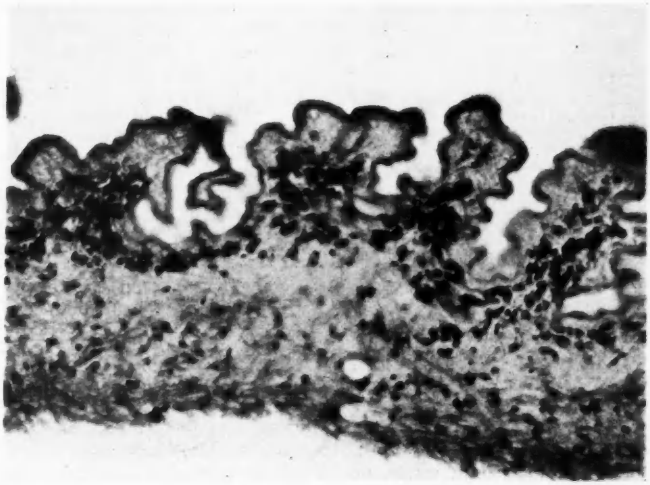

FIG. 4.—Histology of the wall of the racemose cyst shown in fig. 3. Note three distinct layers described in text. (× 320.)

(1) *Outer cuticular layer:* this is a dentate acidophile membrane, averaging 3 μ in thickness. It is arranged in a wavy fashion, the average transverse diameter of each wave being about 20 μ. In places there is a suggestion of ciliation.

(2) *Middle nuclear layer:* this consists of a layer of round to oval nuclei, varying in size from 2 to 5 μ, and numbering from one to twenty.

(3) *Inner parenchymatous layer:* this consists of a reticulum of thin fibrils, throughout which are scattered nuclei similar to those of the middle layer. It averages 40 m μ in thickness.

In the region of the pedicle the appearances are different. The overall thickness is considerably increased, up to 500 μ. The nuclear layer has partially or completely disappeared, leaving the cyst wall with a uniform fibrillary structure, in which many lacunar spaces are seen. In places the expanded fibrillated wall contains irregular masses of hyaline material of varying dimensions. Related to such areas, a reactive capsule of host-tissue origin has formed external to the cyst. The capsule consists of a small amount of collagen, irregular multinucleated foreign-body giant cells and patchy aggregates of round cells, polymorphs and larger mononuclears. In places giant cells have extended into both the cyst wall and the cyst lumen. Eosinophiles are not seen.

Post-mortem appearances.—The body was that of a thin middle-aged female. The scalp and skull showed evidence of the operation described above. An extensive search of the skin, musculature and bone-marrow for evidence of cysticercosis was negative. The heart, lungs and abdominal viscera showed no significant

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macroscopical changes; no tapeworm was present in the bowel contents. The eyes were not examined.

The base of the skull showed moderate erosion of the posterior clinoid processes. The dura mater and its venous sinuses were normal. The pial vessels were congested and the cerebral convolutions slightly flattened. At the base of the brain there was moderate ballooning of the floor of the third ventricle. In the region of the interpeduncular fossa, cerebellopontine angles, and especially the lower part of the roof of the fourth ventricle, the pia arachnoid was thicker, rougher and more opaque than normal. This leptomeningeal thickening partially obscured the markings of the brain-stem and the origins of the lower cranial nerves. The basal arteries and their main branches were normal. The unci of the temporal lobes showed tentorial grooving. No cysts were visible on the surface of the brain and there was no palpable abnormality.

The brain was sectioned coronally after fixation in 4 per cent formaldehyde saline. Areas of gritty resistance, due to the presence of multiple small nodules, were immediately encountered by the knife. These nodules were scattered diffusely throughout both hemispheres and varied from 2–4 mm. in diameter. The majority had a thin, greyish, corrugated, outer capsule, which surrounded a paler centre varying from soft to hard in consistency; a few nodules were unencapsulated. Nodules were located either in the pia in the depths of a sulcus, in the grey matter of the cortex or basal ganglia, or at the junction of grey and white matter. None actually lay free in the white matter (fig. 5).

The most striking lesion (and only true cyst) was in the head of the left caudate nucleus, just beneath the ventricular ependyma (fig. 6). It measured 8 mm. in diameter and was surrounded by a thin greyish capsule. It contained pale-yellow fluid and an irregular, firm, white, mural nodule protruded into the lumen from the posterior part of the capsule.

In all over 30 nodules were counted throughout the brain, eight of these being

FIG. 5.—Intracerebral encysted cysticerci.

FIG. 6.—Encysted cysticercus in head of left caudate nucleus. (The nodule seen projecting into the lumen of the right ventricle represents a further cysticercus.)

in the caudate and lentiform nuclei and the rest in the hemispheres. There were none in the thalami, brain-stem or cerebellum.

There was a moderate symmetrical hydrocephalus involving all ventricles. The ependyma of the left lateral and fourth ventricles showed a patchy, fine granularity, and its vessels were congested. The choroid plexuses were macroscopically normal.

The spinal dura was normal. Many firm white plaques, varying from 1 to 3 mm. in diameter, were scattered throughout the spinal pia-arachnoid over its whole length. These plaques were not adherent to the underlying cord, were unencapsulated and macroscopically different from the nodules in the brain. They appeared to be foci of calcification. The cord itself was normal on section.

Histology (figs. 7 and 8).—Microscopically each cerebral nodule is bounded externally by a capsule of collagenous fibrous tissue which in places is very dense. This capsule shows patchy infiltration with plasma cells and smaller numbers of lymphocytes and large mononuclears; eosinophils are absent. The near-by vessels are congested and a few show endothelial thickening and perivascular cuffing with round cells. At the margin of one nodule, several arterioles show almost complete fibrous obliteration. Around each nodule is a narrow zone of compressed brain tissue. Neuronal changes are insignificant.

Each nodule has a central core of granular and hyaline material, which has a foamy appearance in places. Cholesterol clefts are present. Round or oval bodies staining blue or violet with H. and E., as well as separate granular masses of brownish pigment, are also seen. Fissures, lined by a deeper-staining indented ribbon, are occasionally noticed; these are interpreted as representing the body cavities of degenerate larvæ. The central core is separated from the outer capsule

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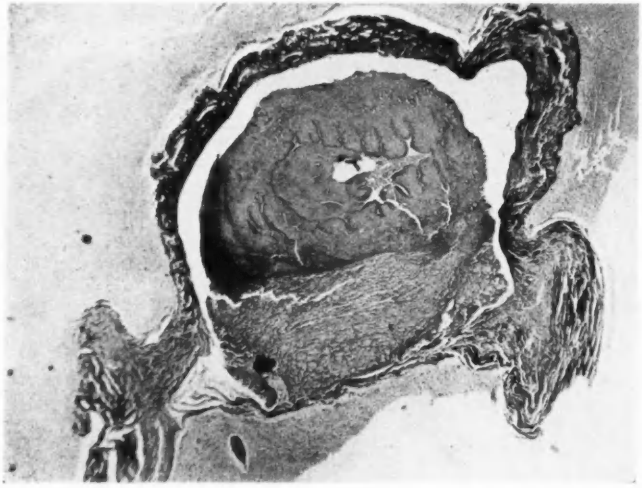

FIG. 7.—Histology of one of the intracerebral nodules, interpreted as showing the degenerate body cavity of a tapeworm larva. (H. & van G.; × 35.)

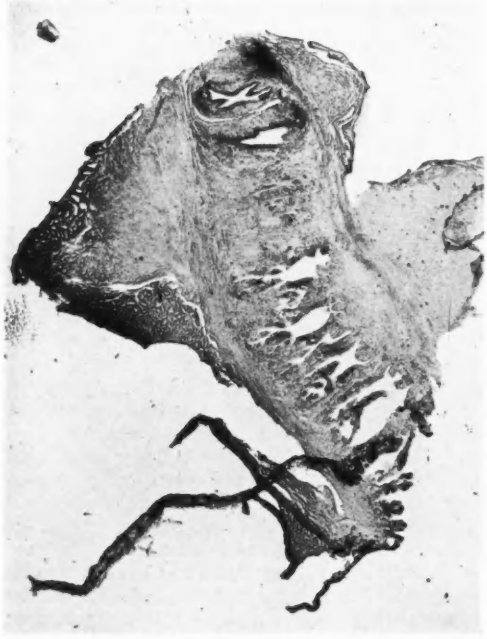

FIG. 8.—Histology of the cyst shown in fig. 6. Note the series of branched clefts representing the invaginated body of a tapeworm larva. (Frozen section; × 10).

by a space, in which foreign body giant cells are found. There is little evidence of calcification. All the lesions examined were markedly degenerate, and no hooklets have been found.

The cystic structure in the head of the left caudate nucleus is less degenerate (fig. 8). An outer fibrous capsule surrounds a definite membrane, identical in appearance to the triple-layered wall of the cyst removed at operation. The cuticular layer of the membrane is outermost and there is a space between it and the fibrous capsule. The posterior mural nodule became detached during technical processing and was sectioned separately. It shows the invaginated body cavity of a tapeworm larva, represented by a series of branched clefts which are lined by a well-preserved nucleated membrane. The intervening tissue contains large numbers of small hæmatoxyphilic bodies. Again no scolex has been seen. Some of the small arteries in the caudate nucleus show endarteritis and perivascular cuffing with round cells, and its ventricular surface shows a well-marked granular ependymitis.

The pia-arachnoid over the convexities of the hemispheres shows both increase in collagen and round-cell infiltration, particularly marked around the vessels, which also show fibrous thickening of all three coats. The pia-arachnoid over the brain-stem shows a similar chronic inflammatory process but to a much greater degree. The lower part of the roof of the fourth ventricle shows extensive fibrous adhesions, in which are embedded fragments identical in structure with the wall of the cyst removed at operation. The choroid plexuses show psammoma body formation, stromal infiltration with plasma cells and lymphocytes, but no evidence of parasitic involvement.

A chronic leptomeningitis is also present in the spinal meninges, diminishing in intensity from the cervical region downwards. Its vessels show fibrous thickening. The nodules in the spinal pia are focal areas of ossification; they are not parasitic structures. The spinal cord shows extensive infiltration with corpora amylacea, especially in the posterior columns, but no other pathological change.

The pituitary gland is normal.

The lungs show early bronchopneumonia and the parenchymatous organs terminal congestion only. No changes are seen in sections prepared from the muscles of the trunk, limbs or diaphragm.

Discussion

It is necessary first to state the grounds on which we consider this to be an example of the racemose form of the *Cysticercus cellulosæ*, for the failure to demonstrate scolices or hooklets in any of the specimens examined has prevented complete identification of the parasite.

The occurrence of late epilepsy in a patient who has lived in India always arouses the suspicion that cerebral cysticercosis is the cause. The length of the history in our patient, the encephalitic episodes in 1943, and the irregular eosinophilia in the blood gave some clinical support to this view. At autopsy, the discovery of (*a*) numerous encapsulated nodules in the brain, each having a degenerate core; (*b*) the presence of the body-canal of a tape-worm larva in sections of the mural nodule found in the cyst in the caudate nucleus, and (*c*) the histological appearances of the wall of the racemose structure removed from the posterior fossa and of the lining membrane of the cyst in the caudate nucleus, both with their three distinct layers, suggesting a similar origin, confirmed the diagnosis of cerebral infestation with tapeworm larvæ. It remained to identify the species of tapeworm responsible.

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The tapeworms whose larval stages are occasionally to be found in man are *T. echinococcus*, *T. saginata*, *T. solium*, and the genus of dog tapeworm Multiceps. There was no resemblance between the findings in our case and those of hydatid disease of the brain, and this was never seriously considered. The cysticercus stage of *T. saginata* (*C. bovis*) has been reported in humans, but according to Faust (1949) all cases except two are very much open to question and in the two confirmed cases there was no involvement of the nervous system.

The larval stage of the Multiceps group presents for us a more interesting comparison, for not only is this particularly likely to be found in the central nervous system, and to cause vertigo ("gid" in sheep), ataxia, fits or hemiplegia, but it may form a racemose structure, examples of which have been found in the spinal cord (Landells, 1949) and at the base of the brain (Roger *et al.*, 1942; Johnstone and Jones, 1950), where it may give rise to attacks of paroxysmal intracranial hypertension. On cursory examination these appear identical with the structure removed from our patient, and with those described by other authors as examples of *Cysticercus racemosa*.

Of the three species which have been said to affect man (*M. multiceps*, *M. serialis*, and *M. glomeratus*) it seems necessary to consider only the first, for Clapham (1941, 1942), who has made a special study of this parasite, believes that *M. multiceps* is indeed the only important species in human helminthology, and that the others are varieties, physiological strains, or developmental stages of this—a view held also by Southwell (1930), Baylis (1932) and Crusz (1948).

Multiceps multiceps forms, however, in its larval stage, not a cysticercus, but a cœnurus. There are marked differences between the two, and also between reported cases of cerebral cœnuriasis and the appearances in our case. Intracerebral cœnuri grow to a considerable size—3 cm. in diameter (Johnstone and Jones, 1950), or 5 cm. or more when fully grown (Mönnig, 1949). Our largest intracerebral lesion had a diameter of 8 mm., in keeping with the statement by Faust (1949) that the *Cysticercus cellulosæ* usually has a diameter of 8–10 mm. Each cœnurus contains many scolices which are invaginated from the cyst wall into cyst cavity (Faust, 1949). These are arranged in clusters and may number as many as 700 (Clapham, 1941). Each cysticercus, however, has only one invaginated larva, and it is further accepted that this larva may be so degenerate as to be unidentifiable as such, although hooklets usually persist. This great difference in the number of scolices no doubt accounts for the fact that the racemose form of cysticercosis is usually sterile (Zenker, 1882; Vosgien, 1911; Fantham *et al.*, 1916; Dolgopol and Neustaedter, 1935), whereas the similar structure formed by *Multiceps multiceps* contains numbers of intact scolices (Johnstone and Jones, 1950). The contents of the racemose cyst in our case was a colourless fluid which, on centrifuging, did not contain scolices or hooklets. The racemose form of cœnuriasis may form elaborate digitate ramifica-

tions at the tips of the buds (Johnstone and Jones, 1950), which have not been described in the reported cases of racemose cysticercosis, and were not present in our case.

There is therefore little doubt that our case was an example of cerebral cysticercosis, and in view of the probability that no other form of cysticercus ever affects the human brain, we submit that there is strong preumptive evidence that we were in fact dealing with the *Cysticercus cellulosæ*. The difficulty in identifying the scolex in any of the lesions examined may perhaps be due to the variable degree of degeneration which was present in each, for it will be recalled that the patient's history was unusually long, being of thirty years' duration.

It has already been noted that the racemose form of cysticercosis has received scant attention in this country, but we feel, from the authorities quoted in the opening paragraphs of this paper, that there is ample evidence that it is not uncommon in other countries, and has been recognized for a long time. As in our case, the well-recognized intracerebral cysts may also occur in the same patient. Fantham *et al.* (1916) state "together with the racemose cysticerci of the basal meninges independent ordinary cysticerci may occur in the brain and the ventricles," while Obrador (1948) writes "these basilar lesions are frequently associated with cortical or ventricular cysts."

The effects of such a lesion, or combination of lesions, are well illustrated in the case reported above. The "attacks" from which the patient suffered were of three types: (*a*) generalized epileptic convulsions; (*b*) attacks of generalized rigidity with loss of consciousness and incontinence but no convulsions; and (*c*) attacks of giddiness, followed by severe headache and vomiting lasting many hours and culminating in loss of consciousness. The first type, which were infrequent, were presumably caused by the cysts localized in the hemispheres. The attacks of rigidity were similar to those seen in lesions of the brain-stem and were presumably associated with the racemose structure in the posterior fossa, which by virtue of its site and mobility, occasionally caused temporary obstruction to the roof foramina in the fourth ventricle and was therefore also responsible for the third type of attack, which were episodes of acute internal hydrocephalus. This structure must have been present from the earliest stage for the first symptoms were of this nature. As early as 1895 Markwald considered that racemose cysticercosis in the region of the fourth ventricle presented a characteristic clinical picture consisting of violent headaches, attacks of vertigo, deep coma and death. These symptoms, often produced by sudden movements of the head, were considered by Bruns (1906) to be diagnostic of cysticercosis of the fourth ventricle, and have been referred to as Bruns' symptom-complex, or Bruns' sign. These features are, of course, referable only to the site of the lesion and not its nature, though a body lying free in the ventricle (such as a solitary cysticercus), or a mobile structure with a long pedicle (such as the racemose form) would be more likely to

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produce such symptoms than other more fixed space-occupying lesions, or mere arachnoidal thickening. That these attacks are not necessarily fatal is shown by our case, and despite the fact that attacks of obstructive hydrocephalus had been occurring for thirty years, no papillœdema had been seen until the last four years, even when the patient had been examined during one of the attacks. Yet on ventriculography there was gross dilatation of the lateral and third ventricles, aqueduct and fourth ventricle. Presumably the obstruction to the flow of cerebrospinal fluid had latterly become permanent whereas previously it had probably been intermittent. Increased obstruction to the normal circulation of fluid was caused as a result of the recurrent episodes of meningo-encephalitis, two of which were observed in 1943. It is important to bear in mind that the rapid loss of sight which often occurs in patients with cysticercosis may be due to the consecutive optic atrophy following papillœdema due to obstruction to cerebrospinal fluid flow in the region of the fourth ventricle rather than to local deposits of cysticerci in the optic nerve, the chiasma, or the eye itself.

Meningo-encephalitis, such as occurred here, with particular affection of the meninges at the base of the brain, has frequently been reported (Schmite and Lemoyne, 1932; Dolgopol and Neustaedter, 1935, Felici, 1938; Arana and Asenjo, 1945; Obrador, 1948; and many others), and it is during this period that a differential count of the leucocytes in the cerebrospinal fluid may show a high proportion of eosinophils. This was not done in our case at the stage of cerebrospinal fluid pleocytosis. The paretic Lange curve associated with a negative Wassermann reaction has been previously recorded on several occasions (Kulkov, 1930).

Mental deterioration is a well-known feature of cysticercosis. In our patient increasing irritability and unco-operativeness made her difficult to live with, and in hospital the series of self-discharges had prevented earlier diagnosis. Latterly, to simple bedside tests of mental function she showed gross impairment. Dixon and Hargreaves (1944) point out that psychic changes are not uncommon, and may range from unco-operativeness, irritability, outbursts of temper and loss of powers of concentration, such as were shown by our patient, to more severe disorders of behaviour, including murder. MacArthur (1934) had already stated that at the Queen Alexander Military Hospital, Millbank, if any breach of ward discipline was reported, a "cysticercosis patient" usually proved to be the delinquent, but he suggested not only that mental disorder was a common symptom of cysticercosis, but that in mental disorder, cysticercosis might commonly be the ætiological factor—"if a commission of persons who had studied this disease, especially in the more elusive forms, were to search diligently lunatic asylums, institutions for epileptics and general hospitals, I think the results would be surprising. If such an inquisition did not bring to light hundreds of unsuspected cases of cysticercosis I should regard this as the greatest miracle since Moses struck the rock." Brailsford (1941) emphatically disagreed with

this, and it seems probable that such an estimate is much exaggerated. Stepién and Choróbski (1949) recently divided the clinical features of cysticercosis into three groups of which the second is constituted largely of patients with mainly psychic manifestations which they attribute to cerebral œdema. Apart from the direct result of the intracerebral parasites, it seems from our case that the loss of cerebral tissue as a result of the severe internal hydrocephalus, and the effects secondary to the changes in the cerebral blood vessels, must also play a large part in this dementia.

The two most striking features in our case were the gross disturbance of equilibration and the involuntary movements.

The former was so severe as to make walking almost impossible, yet on ordinary testing of co-ordination with the patient recumbent only a mild ataxia was demonstrable. These signs were presumably caused by the racemose structure around the brain-stem and extending downwards through the foramen magnum.

The involuntary movements were, however, present continuously, affecting the whole body, of choreic type and sometimes of a magnitude such as is seen in Huntington's chorea. In fact this patient's clinical picture resembled that condition, and it might well be wise to be wary of this diagnosis in a patient who has lived in the East. It is interesting to note that her relatives had commented on these movements for eight years and on her admission in 1946 they were noted as a perpetual restlessness, their true nature and significance not being appreciated. By 1950 they had become the presenting feature of the case and it was no surprise to discover cysticerci in the basal ganglia. Eight were counted in this region and the largest and best-preserved cyst was in the head of the left caudate nucleus (fig. 6). Involuntary movements of this nature do not appear clearly to have been described in cysticercosis though Broughton-Alcock and others (1928) quote Wallenburg (no reference) as saying that automatic movements have been described, and Meyer (1906) described a case with parkinsonian rigidity and tremor in the right limbs. This case also had a racemose cluster around the base. Felici (1938) describes a case with similar parkinsonian features and a cyst in the region of the basal ganglia in whom there was again much evidence of post-meningitic arachnoidal thickening at the base of the brain with cysticerci embedded in the thickened meninges.

In the investigation of the case we have reported there was one feature which we have been unable to explain. On ventriculography the temporal horn of the right lateral ventricle was displaced medially, yet on section of the brain there was no suggestion of such displacement. It is possible that a local œdema of the temporal lobe had occurred prior to ventriculography, but there was no evident reason for this nor any clinical manifestation to support the hypothesis.

It is interesting to consider why in the basal cisterns the lesions produced by the cysticercus tend to a racemose form. The characteristic

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three-layered wall of the cysts show them to be directly attributable to the parasite, yet parasitic structures are rarely found amongst their contents. It seems possible that as a result of recurrent episodes of irritation there is a proliferative meningeal reaction to the parasite. and for purely physical reasons, by virtue of the constant movement of the fluid and the freedom provided by the abundant space, a pedunculated body forms, and extends downwards in the direction of the main flow of fluid. Some support to this view comes from the fact that occasionally such racemose structures are found in the ventricles, e.g. Lamantine de Assis and Tenuto (1948).

Conclusions

The emphasis that has been placed on epileptic fits as the main clinical manifestations of cerebral cysticercosis has, in this country, tended to obscure the fact that symptomatology may be as varied as the areas of brain affected. The clinical features produced by involvement of the meninges in the posterior fossa should receive special attention. By virtue of the site and its relationship to the brain-stem and roof foramina of the fourth ventricle, and the tendency to form the freely mobile racemose clusters, such a variety of transient clinical manifestations is possible, as to cause considerable diagnostic confusion, which may be further complicated by the secondary effects of co-existent intracerebral cysts.

Supratentorial cysts commonly produce epilepsy, though if situated in the basal ganglia may give rise to manifestations simulating parkinsonism, or even more bizarre involuntary movements. Infratentorially the racemose variety assumes greater importance and attacks of unexplained meningo-encephalitis, of "decerebrate rigidity," or of acute obstructive hydrocephalus may all occur, while gross disturbance of equilibration may be an important physical sign.

Loss of vision may be due to cysticerci in the eye or in the chiasmal region, but may also be due to papillœdema and consecutive optic atrophy as a result of obstruction to cerebrospinal fluid flow in the posterior fossa. Mental changes may be due to the direct effects of intracerebral cysts, to the hydrocephalus resulting from posterior fossa lesions, or possibly to atrophic changes secondary to vascular disease. or—as in our case—to a combination of these.

Often no help in diagnosis is obtained from routine investigations and calcification in skull or muscles, eosinophilia in blood or cerebrospinal fluid, or subcutaneous cysticerci may all be absent. Only by bearing the condition constantly in mind will these more difficult cases be recognized, and though in this country it is unlikely to become a common disease, its potential importance is illustrated by Arana and Asenjo (1945) in their figures of incidence in Chile, where during a period of three and a half years they discovered cerebral cysticercosis in 25 of 202 cases investigated as possible brain tumours, i.e. approximately 12 per cent.

Summary

Little attention has been paid in this country to the racemose form of cerebral cysticercosis.

This variety, being particularly liable to occur in the basal cisterns, can give rise to clinical manifestations differing considerably from those usually considered typical of the disease. The better recognized intracerebral encysted cysticerci may be co-existent.

A detailed clinical and pathological study of a case is described, illustrating these features, which include attacks of generalized rigidity, of acute obstructive hydrocephalus, of meningo-encephalitis, and gross disturbance of equilibration. Epileptic fits and bizarre involuntary movements were due to encysted cysticerci in the cerebral cortex and the basal ganglia.

The part played by the racemose form in the production of hydrocephalus, mental deterioration, and blindness is stressed, and points of differentiation given between cerebral cysticercosis and cerebral cœnuriasis.

Acknowledgments

We wish to thank Professor J. Orr, Professor of Morbid Anatomy, University of Birmingham, and Professor J. C. C. Buckley, Professor of Helminthology, University of London, for their advice and criticism, and Messrs. T. F. Dee and F. Bradley for the photographs.

Addendum

Since this article was prepared, four cases of cerebral cœnuriasis have been described in two papers by B. J. P. Becker and S. Jacobson (*Lancet*, 1951, **1,** p. 198, and **2,** p. 1202). They consider that in all cases of infestation of the posterior fossa of the racemose type, cœnurus and not cysticercus is the parasite responsible. Our case, we submit, gives evidence directly contrary to this view. The intracerebral parasites were not cœnuri but cysticerci, each cyst containing one larva only, and unless we are to accept the extremely remote possibility of brain infestation by the larval stage of two totally different tapeworms simultaneously, it seems justifiable to assume that the racemose structure in our case was of cysticercus origin.

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FACTORS INFLUENCING THE COURSE OF REGENERATION AND THE QUALITY OF THE RECOVERY AFTER NERVE SUTURE[1]

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I. Introduction

An analysis of the results of nerve suture reveals great variations in the quality of the recovery even when repair is performed by skilled personnel operating under the most favourable conditions obtaining in the surrounding tissues. What is the explanation of these inconsistent results? Are the failures to be attributed to errors of technique when uniting the severed ends, to delay in repair or to morphological features in the nerve beyond the control of the surgeon? In this paper an attempt will be made to answer these questions by first defining the factors which influence the extent and quality of the recovery following nerve suture: in doing so, the policy will be to establish general principles and not to formulate details of technique. Until these factors have been identified, and the nature and the extent of the influence which each exerts precisely defined, attempts to interpret the incomplete and variable recoveries which follow nerve suture will be subject to considerable error.

It will be shown that several factors always combine to influence the extent and quality of the recovery after nerve repair and that each of these is subject to a wide range of variation from individual to individual, nerve to nerve and, in respect of certain factors, from level to level along the same nerve. For this reason it is necessary, when evaluating a particular procedure or technique associated with repair (e.g. the relative merits of various suture materials and the usefulness of galvanic stimulation in therapy) or when assessing the influence on the end-result of a particular variable (e.g. sepsis and the interval elapsing between injury and repair), to consider each of the several variables that combine to affect the end-result and not to concentrate solely on the particular factor which is the central objective of the investigation. Only by adopting such a policy will it be possible to formulate principles which will make prognosis in these cases less uncertain and will it be possible to evaluate modifications of procedure and technique designed to improve recovery.

The factors which influence the course of regeneration and the extent and quality of the recovery may operate central to the level of the injury, at the suture line or distal to it. Each will be considered in turn.

[1]This work was assisted by a grant from the National Health and Medical Research Council of Australia.

II. Factors Operating in the Peripheral Pathway Proximal to the Lesion

(1) *Retrograde Neuronal Reaction and Degeneration*

The essential feature of regeneration in peripheral nerve fibres is the outgrowth of axons to replace the processes which have perished as a result of the injury. Such regrowth requires the survival of the nerve cells whose processes have been injured. It is well known, however, that section of an axon may cause profound changes in the parent cell which are characterized by swelling, dissolution of the Nissl granules, vacuolation of the protoplasm and dislocation of the nucleus from the centre. The final result of these changes may be the death of the cell, its return to normal within 40 to 120 days or the persistence of a residual defect which reduces its efficiency.

Though the nature of the central disturbance induced by the injury is unknown it seems reasonable to assume that it will influence the capacity of neurons to provide new pathways to the periphery. In this connexion the following information is of significance.

(i) Section of an axon may fail to leave an impression on the parent cell which can be detected by the methods at present available (Marinesco, 1898*a*; De Neef, 1901; van Gehuchten, 1906; Bucy, 1928; Geist, 1933; Romanes, 1941, 1946). There is no explanation to account for the occurrence of chromatolysis in some cells and the complete absence of any signs of it in others of the same functional group. Marked variations in vulnerability are apparently due to specific physical and chemical differences in the cytoplasm which have not yet been demonstrated.

(ii) There is a considerable variation in the rate of chromatolysis and recovery in different neurons of the same functional group (Barr and Hamilton, 1948).

(iii) The intensity of the reaction varies from individual to individual and at different ages in the same species (Geist, 1933). Thus neurons undergo a much more rapid and complete degeneration after nerve injury in the young than in the adult (Vulpian, 1868; Gudden, 1870; Hayem, 1873; Mayser, 1877; Forel, 1887; Homén, 1890; Pellizzi, 1892; Warrington, 1898; Ranson, 1906; d'Abundo, 1914; Brodal, 1940).

(iv) The greater the violence to the axon the more intense the reaction. Thus it is more intense when the nerve is avulsed than when it is cut or ligated (Forel, 1887; Marinesco, 1898*b*; van Gehuchten, 1906; Nicholson, 1924; Bielschowsky, 1932). Marinesco (1901) used graded degrees of violence in applying stretch to nerves and found the reaction to be proportional to the violence.

(v) The intensity of the reaction varies inversely as the distance of the site of the damage from the cell (Bielschowsky, 1932; Geist, 1933). Thus it is greater in lesions of nerve roots than of nerve trunks. According to Buzzard and Greenfield (1921) "spinal nerves may be divided in

peripheral parts of the limbs, and a search for cell changes may give very meagre or no results."

(vi) In proximal injuries the neurons innervating the most distal segment of the limb are the most severely affected (Hayem, 1873; Dreschfeld, 1880; Homen, 1890; Pellizzi, 1892; Romanes, 1941, 1946).

(vii) The reaction occurs more rapidly (Fleming, 1896, 1897) and is more severe in sensory than in motor cells (van Gehuchten, 1906; Bucy, 1928; Romanes, 1946) and more especially in the small cells of the spinal ganglia (Ranson, 1906, 1909).

(viii) Estimates of the number of cells perishing after nerve division vary. Ranson (1906, 1909) reported a loss of 52 per cent in the spinal ganglia. The following losses have been reported for the anterior horn: Knape (1901) 20 per cent; Goering (1928) 83 per cent; Turner (1943) 16 per cent; Romanes (1946) exceeding 40 to 50 per cent; and Barr and Hamilton (1948) 6 per cent.

(ix) Marinesco (1898*c*) claims that the recovery of the neuron from chromatolysis depends upon the union of the central and distal stumps of the severed nerve, but this is denied by Warrington (1899), Lugaro (1904), van Gehuchten (1906), Bucy (1928) and Bielschowsky (1932).

(x) The restoration of those structural details which are believed to represent the normal state may be delayed for periods exceeding 136 days (Barr and Hamilton, 1948).

(xi) The retrograde disturbances may extend beyond the cell originally involved by inducing trans-synaptic effects in related neurons (Marinesco, 1892; Onuf, 1895; Warrington, 1898, 1899, 1900; Anderson, 1902; van Gehuchten, 1906; Marinesco, 1909; Gägel, 1930; Sherrington, 1932; Kahr and Sheehan, 1933; Foerster and Gägel, 1934; Romanes, 1946; Penman and Smith, 1950). In this way the functions of whole groups of neurons may be impaired and even their very existence jeopardized.

(xii) It is conceivable that the persistence of retrograde and trans-synaptic effects may adversely affect complicated patterns of activity. Campbell (1944) has described the loss of the proprioceptor component of the segmental spinal reflex during the period of chromatolysis which follows section of the ventral roots of peripheral nerves in the cat.

The following conclusions may be drawn from these observations.—(*a*) After the severance of a peripheral nerve some neurons remain unaffected, others undergo profound changes which culminate in disintegration, while an intermediate group shows a retrograde reaction of varying severity which is partly or fully reversible. Retrograde degeneration represents a permanent reduction in the number of cells which are to provide the new pathways to the periphery while it is reasonable to assume that variations in the intensity of the reaction, the time taken for recovery to occur and the degree of any residual defect will affect the rate, extent and quality of the recovery. Unfortunately there is no way of accurately evaluating the extent and severity of the retrograde changes in any individual patient. An analysis of the end-

results in a series of clinical cases does not provide absolute information on this point. Recovery is never complete after nerve repair and because several factors operate simultaneously to influence the quality of the recovery, it is impossible to estimate how much of the residual defect should be attributed to any particular factor. On the basis of the experimental evidence, however, it may be expected that:

(i) the retrograde effects will be more severe after high than after low lesions and will be directly proportional to the severity of the causative injury;

(ii) the preparation of the proximal stump for suture must induce further retrograde changes in the surviving cells;

(iii) retrograde effects will be more serious in sensory than in motor neurons. Sensory recovery will therefore be slower and less satisfactory than motor recovery.

(*b*) Variations in the retrograde neuronal reaction in the form of degeneration, delayed recovery, incomplete recovery and persistent trans-synaptic effects, may contribute to the observed variations in:

(i) the distances over which retrograde Wallerian degeneration occurs in the proximal stump;

(ii) the interval before regeneration commences, the onset being delayed for longer periods when the cell is more severely affected;

(iii) rates of regeneration. Thus axons regenerate more slowly after nerve suture than after simple injuries;

(iv) the extent and quality of the recovery.

(2) *Regenerative Power of Neurons which Survive Severance of their Processes*

Holmes and Young (1942) have shown experimentally that the surviving axons in the central stump of severed nerves retain the capacity to sprout "after nearly a year from the original injury," which was the period covered by their experiments. Duncan and Jarvis (1943) state that this capacity is "essentially inexhaustible" in the cat, the vigor and speed of new growth being undiminished after repeated injury. There is much clinical evidence to indicate that this capacity is retained for several years in human nerves. Of more importance than the capacity of the neuron to sprout, however, is its capacity to spin a new axon right to the periphery and, on re-establishing continuity with an appropriate end-organ, to excite satisfactory function in the reinnervated tissue. This alone can be accepted as an expression of its full regenerative power.

The maturation of the new axon pathways, on which depends the restoration of their functional efficiency, involves morphological changes of a highly complex character. These are little understood though it is generally believed that they include such processes as myelination and the restoration of the calibre of the fibre. If this be so, then any factor which restricts these processes should permanently impair the function

of the new fibre. Such factors could operate at one or a combination of the following four sites: (*a*) the parent neuron, (*b*) the suture line, (*c*) the peripheral segment and (*d*) the neuromuscular and neurosensory connexions. Only the first will be considered in this section.

The precise role which the parent neuron plays in the maturation of the regenerated fibre is still obscure. The results of experimental work, however, favour the belief that regenerating axons derive their characteristics from the parent cells rather than from their peripheral connexions.

Detailed clinical data relating to this feature indicate that the capacity of *some* neurons to regenerate functionally efficient pathways is fully retained for at least twelve months (Sunderland, 1949, 1950). Whether this desirable property is retained indefinitely remains unanswered though there is some presumptive evidence in the clinical literature that it is retained for periods exceeding twelve months. Unfortunately, precise measurements of the quality of the recovery have not been recorded for those patients in whom the interval between injury and repair exceeds this limit. Furthermore, because several factors operate simultaneously to influence the extent and quality of the recovery after nerve repair, it is impossible, where recovery is incomplete, to estimate how much of the residual defect should be attributed to retrograde neuronal changes. Compensatory mechanisms leading to full recovery in incompletely reinnervated muscles may also obscure the persistence of impaired neuronal activity. Compensatory mechanisms, however, could not alone account for complete recovery. Therefore, the clinical observation that some muscles which have been denervated for at least a year recover completely indicates that the recuperative powers of *some* neurons are fully retained for this period (Sunderland, 1950).

Factors operating at central levels which modify the conversion of the restored pathway into an efficient fibre system.—Abnormal influences which adversely affect the conversion of the restored pathway into an efficient fibre system may, however, operate at neuronal levels in the following ways:

(i) Incomplete recovery of the neuron from retrograde or transsynaptic effects may reduce its capacity to restore the outgrowth to its original diameter and degree of myelination.

(ii) An increase in the number of processes under the influence of the neuron as the result of axon budding during regeneration may, by dissipating its resources, prevent the cell from exerting its full influence on any one fibre. The extent to which this adversely influences maturation is conjectural, however, particularly in view of the evidence that branching of nerve fibres normally occurs along the length of a nerve (*see later*). Nevertheless it is conceivable that axon budding and branching may reach such abnormal proportions that the maturation of pathways is seriously jeopardized.

(iii) The length of the regenerated fibre under the influence of the

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neuron may be a factor affecting maturation and its capacity to function efficiently. During regeneration the axon of an originally short nerve fibre may enter, by erroneous cross-shunting at the suture line, an endoneurial tube originally occupied by a long fibre. When this occurs it is known that the regenerating axon will grow the full length of the endoneurial tube which it enters. In this way a neuron originally controlling the activities of a short fibre is now called upon to administer to the needs of a process of considerable length and it is conceivable that under these conditions the energies of the neuron may be dissipated along the length of the fibre. The extent to which this aberrant regeneration is compatible with efficient function remains obscure.

(3) *Factors other than Retrograde Phenomena which Affect the Capacity of Neurons to Create New Processes*

Age.—The results of Gutmann and his associates (1942) indicate that the rate of advance of axon tips down the nerve is of the same order in both young and old and that the rapid recoveries observed in young animals are more likely to be due "to great shortening of the delay in the suture scar, and probably acceleration of functional completion, combined, of course, with the fact that the distances to be covered are small." Whether or not the course of regeneration of human nerves is affected by the age of the patient remains unanswered. Furthermore there are not yet sufficient data to permit an evaluation of the influence of age on the quality of the end-result. However there is some presumptive evidence that the very young enjoy certain advantages which contribute to better recoveries than are observed, other things being equal, after repairs in adults (Platt, 1943; Elkington, 1944; Souttar, 1945; Zachary and Holmes, 1946; Björkesten, 1947; Sunderland, 1949). This finding conflicts with the observation that nerve severance is followed by a more severe retrograde reaction in the young than in the adult.

Toxic and metabolic factors.—The vitality of the neuron is influenced by metabolic substances in the body fluids and by the presence of toxins. The extent to which regeneration of injured nerves could be affected by such factors is not known (Weiss, 1944).

Temperature.—Deineka (1908) expressed the belief that a rise in temperature increased the activity of regeneration. However the thermal variations between summer and winter appear to be without effect on the regenerative processes in human nerves (Sunderland, 1947*a*).

(4) *General Conclusions*

Retrograde and trans-synaptic changes adversely affect regeneration and limit recovery by (i) reducing the number of axons available for regeneration, (ii) disturbing the function of restored pathways, and (iii) modifying patterns of activity and in this way rendering them less efficient. The changes are more severe in sensory than in motor neurons,

in the young than in the adult, after high lesions as opposed to injury in the distal part of the limb while they increase with the severity of the trauma to the nerve. These variables are all beyond the reach of therapy and the skill of the surgeon though the latter should remember that additional damage to the proximal stump during the preparation of the nerve ends for repair aggravates the retrograde effects, particularly when a careless and rough technique is employed. Because of the widespread effects created in the nervous system by localized trauma it is imperative that this tissue should be treated at all times with the greatest respect.

However not all neurons suffer irreparable injury as the result of severance of the nerve. The recuperative powers of many and their capacity to regenerate functionally efficient pathways are fully retained for at least twelve months.

III. Factors Operating at the Suture Line

For convenience the factors operating at the suture line may be subdivided into groups which influence the entry of axons into (1) the distal stump, (2) the funiculi of the distal stump, and (3) appropriate endoneurial tubes which is necessary for the re-establishment of the original fibre pattern.

(1) *Factors Influencing the Entry of Axons into the Distal Stump*

(A) *The nature of the tissue intervening between the sutured nerve ends.*—In order to reach the distal stump regenerating axons must traverse the tissue which joins the nerve ends. This bridging tissue is never as suitable a medium for the growth of axons as are the endoneurial tubes and, varying as it does in density, arrangement and amount, represents a zone where the axons may be obstructed or delayed in their passage distally. Least resistance is offered to the advancing axons when its constituent fibrils are arranged in parallel strands along which the axons can glide freely and in the appropriate direction. At the same time the tissue must be so constructed that it is sufficiently strong to retain the nerve ends in permanent apposition.

To achieve this desirable effect it is necessary, when performing end-to-end suture, to remove all incompatible tissue by the suitable preparation of the nerve ends and to adopt a technique which will, despite individual peculiarities of scarring, restrict and not aggravate the formation of tissue which is antagonistic to regeneration. This implies:

(i) the most gentle handling of the nerve and particularly of the nerve ends;
(ii) complete asepsis;
(iii) care in the mobilization of the nerve and the preservation of an efficient blood supply to the nerve ends (Sunderland, 1945*a*, 1949);
(iv) the avoidance of undue operative and post-operative tension at the suture line, which will cause separation of the nerve ends

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and an increase in the intervening scar tissue. This is achieved by a combination of mobilization and rerouting of the nerve which should involve as little intraneural disturbance as possible;

(v) a suitable bed for the nerve in which the suture line is not subjected to undue movement and friction and where the formation of anchoring and distorting adhesions will be avoided or minimized;

(vi) the employment of suture materials and a suture technique which excite a minimal reaction in the host tissues. The results of an experimental examination of the suitability of existing suture materials for repairing nerves and the principles which should govern the method of application of sutures have been detailed elsewhere (Sunderland and Smith, 1950).

(B) *The relative dimensions of the nerve ends.*—Having penetrated the bridging tissue the axons must next enter the distal stump if they are to reach the funiculi and their contained endoneurial tubes. Whether they will do this or pass outside it largely depends on the relative dimensions of the opposed nerve ends.

Investigations have shown that the proximal stump of a severed nerve does not shrink and may even undergo a slight enlargement. On the other hand the distal stump suffers a reduction in its cross-sectional area. The rate at and the extent to which this atrophy occurs, and the manner in which the process is influenced by variations in the relative amounts of the funicular and connective tissues composing the nerve have been investigated (Sunderland and Bradley, 1950*a*). The funicular atrophy, which follows the disintegration and removal of the axons and myelin, increases with the duration of denervation, rapidly at first and then more slowly. There is a 40 to 50 per cent loss at 60 days, a 50 to 60 per cent loss at 90 days, while at 140 days the residual funicular cross-sectional area is 30 to 40 per cent of its original value; beyond this point there is no further significant change. The supporting epineurial connective tissue, on the other hand, does not react in the same way and in comparison undergoes little change.

Since the funicular and epineurial tissues react quite differently to denervation it follows that the extent of the shrinkage of the nerve trunk will be greatly influenced not only by the duration of denervation but also by the percentage cross-sectional area of the nerve devoted to the funiculi. Investigations (Sunderland and Bradley, 1949) have shown that this morphological feature is subject to considerable variation, the funiculi being more compactly arranged in some regions than in others depending on the looseness of the supporting epineurial framework and the amount of fat which it contains. For these reasons the atrophy would be greater where the nerve was composed of tightly packed funiculi with little supporting tissue than where the funiculi were widely separated by a large amount of epineurial tissue. Consequently the reduction in the cross-sectional area of the entire nerve will not parallel the funicular

atrophy but will show irregular fluctuations which are determined not only by the duration of denervation but also by relative amounts of the funiculi and supporting connective tissue at the site of the repair.

Despite these irregularities it is important to remember that:

(i) there are occasions when the atrophy of the distal stump is such that many regenerating axons fail to enter it;

(ii) given a constant funicular pattern, the atrophy of the distal stump increases progressively with the duration of the denervation until the fourth month after which there is no further significant change.

A practical point of interest in this connexion is that the funiculi and connective tissue may be so proportioned at the site of severance that the denervation changes, though profoundly affecting the funiculi, would result in only a slight reduction in the cross-sectional area of the distal stump. End-to-end suture under these conditions might, in the absence of a cross-sectional analysis of biopsy material, give the erroneous impression that good apposition had been obtained when, in effect, the pre-existing disparity in the funicular patterns would have been grossly accentuated by the atrophy of the bundles in the distal stump. As a result, many regenerating axons would fail to reach funiculi and their contained endoneurial tubes.

(2) *Factors Influencing the Entry of Axons into the Funiculi of the Distal Stump*

Advancing axons make useful connexions with the distal stump only when they enter the endoneurial tubes comprising the funiculi. Factors influencing their entry into the funiculi are (i) the funicular patterns of the nerve ends, (ii) the cross-sectional area of the nerve trunk occupied by the funiculi and (iii) the extent of the denervation funicular atrophy.

(A) *The funicular patterns of the nerve ends.*—Any dissimilarity of the funicular patterns of the nerve ends favours the overlap of bundles and the wasteful regeneration of axons into the interfunicular spaces of the distal stump.

It is uncommon for human peripheral nerves to be composed of a single funiculus. They are, on the contrary, usually composed of several funiculi which, by their repeated division and anastomosis, engage in plexus formations along the full length of the nerve. As the result of these changes, the number, size and arrangement of the funiculi vary from level to level, while the funicular pattern is altered so rapidly that transverse sections taken more than a few millimetres apart fail to present precisely the same pattern. Thus after the destruction of even a few millimetres of nerve, either by the injury or in the preparation of the nerve ends for repair, there will be a dissimilarity in the funicular patterns which will favour the wasteful regeneration of axons into the

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interfunicular spaces of the distal stump. The amount of the funicular overlap is increased when the bundles are small and numerous. On the other hand it is diminished at levels where the bundles are large and few in number.

(B) *The cross-sectional area of the nerve trunk occupied by the funiculi.*—In addition to the variation in the number, size and arrangement of the funiculi brought about by plexus formations, peripheral nerves present individual, lateral and regional differences and peculiarities as regards the proportion of the cross-sectional area of a nerve trunk occupied by its component funiculi. The epineurial tissue likewise varies in amount along the length of the nerve. In addition, at any level the percentage funicular area varies inversely as the number of funiculi. Despite these variations there is normally a large amount of connective tissue separating the funiculi. This information has been detailed elsewhere (Sunderland and Bradley, 1949), and for the purposes of the present discussion it will suffice to state that the funiculi of human nerves are more compactly arranged in some regions than in others and that in some specimens the bundles are small and are widely separated.

Despite the dissimilarity of the funicular patterns of the nerve ends, end-to-end apposition of funiculi may still be attainable during repair, and the chances of restoring useful connexions consequently improved, when the funiculi are few in number and are tightly packed since there will then be less interfunicular tissue into which regenerating axons may be directed. On the other hand, when suture is performed in a zone where the funiculi are more numerous but small and widely separated, the possibility of some funiculi being unavoidably directed towards the interfunicular spaces is considerable. When this occurs many regenerating axons enter the interfunicular spaces and there end blindly. Recovery under such circumstances is less complete and the prognosis consequently worse.

Following suture of a severed nerve, the number and degree of separation of the bundles therefore becomes a factor affecting the entry of regenerating axons into the endoneurial tubes of the funiculi of the distal stump and in this way a factor influencing the extent and quality of the recovery. On the basis of these two features it has been possible to arrange the various peripheral nerves in order of merit as regards the favourability or otherwise of the local conditions for recovery. Furthermore, because of regional differences in the same nerve, it has also been possible to indicate zones where conditions favour the loss of axons in the manner indicated and zones where such a loss would be reduced. Even when the percentage funicular area is maximal, however, there is still sufficient interfunicular connective tissue to result in the wasteful escape of some axons. This information has been detailed elsewhere (Sunderland and Bradley, 1949).

(C) *The extent of the denervation funicular atrophy.*—The entry of regenerating axons into the funiculi is rendered more difficult by the

funicular shrinkage described in an earlier section. On the basis of the observations reported there is good reason for believing that the chances of restoring useful connexions with the distal stump diminish progressively for the first four months of denervation, after which the conditions remain substantially the same.

Funicular shrinkage also leads to a concentration of the endoneurial tubes per unit area. As a result the tubes in a unit area will have fewer axons reaching them than would otherwise be the case. Fibre branching and attractive influences from the distal stump (if the latter do operate) may offset this to some extent but in any event the arrangement is one which will add to the confusion of the fibre pattern.

(3) *Factors Influencing the Entry of Regenerating Axons into Appropriate Endoneurial Tubes*

The restoration of function requires something more than the regeneration of axons, their entry into endoneurial tubes and their passage to the periphery. In order to achieve full restoration of function the original fibre pattern must be completely restored during regeneration. This unfortunately never occurs owing to the inevitable erroneous cross-shunting of axons and the failure of others to reach the funiculi of the distal stump. It is important, therefore, to know the factors which affect the reconstitution of the fibre pattern since it is upon this knowledge that an understanding of variations in the quality of the recovery after nerve suture greatly depends. These factors are:

(A) The manner in which the axons approach the distal stump.

(B) The intraneural arrangement of the nerve fibres at the suture line.

(C) The number of fibres at the level of the suture line representing individual branches.

(A) *The manner in which the axons approach the distal stump.*—After the severance of a nerve the fibres of the proximal stump undergo a retrograde degeneration which extends for variable, but often considerable distances. This degeneration differs in no significant respects from that observed below the lesion with the result that empty endoneurial tubes also appear central to the lesion. Unlike those in the distal stump, however, each of these contains an axon tip at its top end. At the commencement of regeneration each surviving axon therefore travels within its original endoneurial tube as far as the level of the lesion with the result that regeneration proceeds in an orderly fashion and the fibre pattern is fully retained. Whether regenerating axons will, in the absence of any division of the tube, branch in the initial part of their descent is unknown. If, however, obstruction to the passage of an axon is the sole stimulus to multiple budding then the latter should not occur unless obstructing degenerating remnants are retained in the tubes. Frequently, however, tubes are seen in the proximal stump each of which contains

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several axon outgrowths in the absence of any obstruction (unpublished observations).

At the suture line the axons enter a new environment which is composed, essentially, of Schwann cells and fibroblasts. The direction taken by the advancing axon tips and the manner in which they approach the distal stump are determined solely by the arrangement of the fibrillar units which comprise the bridging tissue. Under ideal conditions these are so orientated during their formation that they guide the advancing tips in an orderly fashion and in the appropriate direction. Any deviation from this pathway pattern will, by diverting and barring the passage of axons, result in confused nerve growth.

It would be interesting to know when the Schwann and fibroblast tissue strands become converted into a morphologically definitive sheath about the regenerating axon. In this connexion there are at least three possibilities.

(*a*) The tube could be preformed in advance of the axons so that the latter would be confined within endoneurial tubes from the onset of regeneration until each entered the distal stump. The new fibre pattern would therefore be determined by the manner in which the Schwann strands from above and below became associated and later converted into tubes. Any confusion of the fibre pattern occurring under these conditions would therefore have, initially, a Schwann cell basis. Furthermore axon sprouting would be restricted to individual tubes and such sprouting could not increase the potentialities of repair by increasing the chances of possible connexions between the two nerve ends. There is, however, no evidence to support this hypothesis.

(*b*) The new tube could be elaborated simultaneously with the descent of the axon.

(*c*) The changes which result in the elaboration of definitive sheaths may be delayed until the axons have entered the distal stump.

There is good evidence that the third mechanism is operating though there is less certainty about the participation of the second (Cajal, 1928). In any event any mechanism which does not restrict axon growth to preformed tubes leaves them free to multiply and wander within the tissues of the suture line, the direction they take being governed solely by the structural characteristics of the tissue in which they are moving. As a result they are easily deflected by malaligned fibrils and this adds to the possibilities of fibre mixing. Furthermore under these conditions the axon tips, on reaching the face of the distal stump, are free to explore it and to compete for the endoneurial tubes which it contains.

Though our knowledge of the movement of axons across the suture line is still incomplete it may be accepted that:

(i) The direction taken by the advancing axon tips is determined by the organization of the bridging tissue. Nerve fibre wandering and mixing are minimal when the fibrils are arranged in parallel strands along which

the advancing axons can move freely and in the appropriate direction while they are increased when the fibrils are densely packed in an oblique transverse or irregular fashion.

(ii) Axons may multiply on their way to the distal stump. Whether this is due solely to the stimulus provided by obstruction or to other factors remains unknown.

(iii) Axons may compete for endoneurial tubes in the distal stump. The arrangement of the junctional tissue only directs them to the stump face. Once there, they are free to explore the nerve face for a suitable path distally.

(B) *The intraneural arrangement of the nerve fibres at the suture line.*—The extent to which the fibre pattern is restored largely depends on the manner in which the fibres are arranged in the nerve at the level of the repair. To appreciate this, reference must first be made to the manner in which the funicular plexus formations effect a regrouping and funicular redistribution of the component nerve fibres as they are traced proximally from the point where they leave the nerve trunk as individual branches (Sunderland, 1945*b*; Sunderland and Ray, 1948).

The fibres representing individual branches at first pursue an independent course either as a single funiculus or as a compact group of funiculi engaging in plexus formations. Over this part of their course the fibres are consequently sharply localized though they do not necessarily maintain the same quadrantic relationship as they ascend since migration sometimes carries them obliquely through or over the surface of the nerve.

The bundles of adjacent but independent bundle groups subsequently anastomose, thereby effecting a blending of the constituent fibres of originally distinct groups. An extension of this process ultimately results in the widespread diffusion and blending of fibres from several sources. The scattering of fibres produced in this way occurs gradually, however, and over a short distance only a minor degree of intraneural shift is effected. It is the summation of changes at successive levels as the intercommunications are repeated which is ultimately responsible for the widespread intermingling and dispersal of fibres. The latter is achieved, therefore, only after the fibres have ascended considerable distances along the nerve. Thus the localization of any particular branch system is at first discrete, then discrete in combination with other fibres, and finally a predominant one only until fibre-diffusion reaches a stage where it cannot be claimed that there is any localization; at this stage, the constituent fibres of the bundles are arranged in varying combinations and proportions though each bundle does not necessarily contain fibres from all branches.

For these reasons the longer the course of the fibres of a branch within a nerve trunk, the greater the diffusion and the intermingling of its fibres at proximal levels. When, however, the bundles of a branch with

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a very high origin commence to anastomose they do so with bundles which have acquired fibres from most, if not all, of the distal branches. As a result the fibres of such proximal branches are rapidly mixed with those from several sources but, since their intraneural course is too short to permit extensive scattering, they remain relatively discretely localized.

Nerve funiculi are, therefore, of two types and both occur together at the same level. There are those which are composed solely of fibres from one branch while the others contain fibres from several sources in varying combinations and proportions.

The amount of fibre mixing occurring during regeneration depends principally on the extent of the localization of individual branch systems at the level of repair. For convenience the results of regeneration occurring where the localization is sharp and where the fibres from all or several branches are mixed will be considered separately. Naturally intermediate patterns occur but they do not materially affect the discussion.

Factors affecting the restoration of the fibre pattern when the branch fibres are separately and sharply localized: Where individual branch fibres are sharply localized to separate funiculi regenerating axons will be directed towards corresponding tubes providing funicular apposition is suitable and the axons are not diverted from their appointed course by deflecting strands in the bridging tissue.

Factors affecting the restoration of the fibre pattern when fibres from several different sources are intermingled: Detailed information is still lacking on the manner in which new, and therefore additional, endoneurial tubes are elaborated in the distal stump either from the component tissues or as the result of a multiplication of those already present. Weiss (1944) has described Schwann cells appearing in intertubal positions in the distal stump but whether these can be utilized for the elaboration of new tubes is unknown. Holmes and Young (1942) have reported that: "Two, three, or even more fibres may medullate within a single tube, and it may be that each acquires its own neurilemma and endoneurium, dividing up the original tube. But it is very difficult to make certain whether the transition from this condition to the normal regenerated nerve involved a true creating of several nerve fibres from within a single old tube, or whether some of the supernumerary fibres are later destroyed even though they have become to some extent myelinated. In the majority of the tubes there is only a single fibre left when medullation is well advanced." In view of the prevailing uncertainty it may be accepted that there is no increase in the number of endoneurial tubes which extend to the periphery and preserve the outlines of the original pattern of innervation. Since the latter is so inseparably bound up with the original tubal pattern it follows that only those axons which enter tubes already present can participate in the reinnervation of the pattern. Though axons which fail to make such an entry acquire new sheaths these develop *pari passu* with the growth of the axon, bear no relationship to

the original pattern, and are therefore unable to provide a guide to the periphery. The development of new tubes does not, therefore, aid regeneration.

Since the useful tubes in the distal stump remain unchanged it follows that the regenerating axons will compete for them. Under these conditions, and where the fibres innervating different structures are intermingled, the entry of axons into original or functionally related tubes is complicated by (i) variables associated with the growth of the axon to and across the suture line, and (ii) the extent of the post-traumatic atrophy of the endoneurial tubes.

(i) *Variables associated with the growth of the axon to and across the suture line:* These comprise (*a*) the delay before different axons commence to regenerate; (*b*) the distances to be covered before individual axons reach the distal stump; (*c*) the relative rates of growth of different axons in the proximal stump and across the suture line; (*d*) the amount of multiple sprouting which occurs; and (*e*) the direction of axonal movement across the suture line.

(*a*) *The delay before different axons commence to regenerate:* If the severity of the retrograde reaction influences the onset of regeneration all axons may not commence advancing simultaneously because in any injury the trauma sustained by individual nerve fibres may vary. The onset of regeneration may be unduly delayed in some axons in comparison with others and as a result these will be at a disadvantage during the early stages of regeneration in that others reach and compete for the tubes before they have an opportunity to do so.

(*b*) *The distances to be covered before individual axons reach the distal stump:* Following severance of a nerve the fibres of the proximal stump are involved in a retrograde degeneration which extends for different distances in different fibres. The factors controlling the extent of this central degeneration in individual fibres are unknown but presumably they are bound up with the severity of the injury. However, as a result of these changes all axons do not commence sprouting at the same level. This means that some have longer distances to travel before reaching the distal stump than others so that those which arrive first are in a position to establish a prior claim on the tubes. Though this may not prevent others entering at a later date, it must complicate such entry.

(*c*) *The relative rates of growth of different axons in the proximal stump and across the suture line:* The rate of regeneration is influenced by the type and consistency of the tissue joining the nerve ends and by the distance of the lesion from the cell body (Sunderland, 1947*a*). The tissue at the suture line rarely presents a uniform structure so that some axons may have to overcome obstacles which will delay them in their passage to the distal stump. As a result of their late arrival these will be at a disadvantage in the competition for tubes.

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(*d*) *The amount of multiple sprouting which occurs:* The development of multiple offshoots from surviving axons which occurs at the onset of regeneration increases the potentialities for recovery by (i) compensating for the loss of some axons due to retrograde changes and the failure of others to enter endoneurial tubes, and (ii) providing a variety of seekers to explore the best available route to the endoneurial tubes. Such sprouting may, however, reduce the quality of the recovery by adding to the distortion of the fibre pattern which is produced by the erroneous cross-shunting of regenerating axons. Another disadvantage is that during regeneration multiple sprouts from either a single or different axons may enter the same tube simultaneously. Only one of these ultimately survives though the reason for this is unknown nor has it been determined whether the surviving axon is that which first reaches the end-organ or that which is most closely associated anatomically and functionally with the tube. In any event, the occupation of one tube by axons from different cells and the ultimate atrophy of all but one axon adds to the fibre loss which occurs during regeneration.

Little direct information appears to be available as to whether or not multiple sprouts from the *same* axon can, on entering different tubes, each survive and grow distally. That such may occur, however, is supported by the observation that peripheral nerve fibres normally divide as they travel peripherally (Lavarack, Sunderland and Ray, 1951) while this also occurs during regeneration (Langley and Anderson, 1904; Kilvington, 1905; Osborne and Kilvington, 1909; Greenman, 1913; Langley, 1917; Aird and Naffziger, 1939; Kilvington, 1941; Gutmann and Sanders, 1943; Hillarp and Olivecrona, 1946). Such regeneration may, however, complicate recovery by leading to a dissipation of the energies of the neuron over several pathways so that it is unable to direct the normal activity of any one of them. Whether adjustments can occur to compensate for this is unknown.

It is also not known whether all regenerating axons branch to the same degree or whether some are superior to others in this regard and, if so, the factors which influence the amount of branching and the manner in which it is brought about. If the amount of branching varies it follows that those fibres showing maximal sprouting have a decided advantage in the competition for tubes.

(*e*) *The direction of axonal movement across the suture line:* The extent to which the regenerating axons are deflected from the course which would take them towards their corresponding tubes is determined by the organization of the bridging tissue. The significance of this factor has already been discussed.

(ii) *The extent of the post-traumatic atrophy of the endoneurial tubes.*— The contents of the endoneurial tubes fluctuate in both quantity and composition with the various phases of degeneration but ultimately they are entirely the products of Schwann cell proliferation. The lumen of

each tube commences to shrink as the breakdown and removal of the myelin and axoplasm nears completion. This shrinkage occurs rapidly at first, and then more slowly until approximately the third month after which little further change occurs (Sunderland and Bradley, 1950*b*). The fibres are affected in proportion to their diameters, the largest being reduced to endoneurial tubes filled with Schwann cells while the smallest become converted into fine strands. Thus at and after the third month the funicular face is composed of a mass of tissue representing endoneurial-Schwann strands scattered in small numbers among which are endoneurial-Schwann tubes of variable diameter the largest of which, however, rarely exceed 3 μ.

It would be interesting to know how the regenerating axons behave when they are confronted with this tissue. It is possible that the first to arrive would claim the tubes rather than the bands. If such be the case the largest tubes are more likely to be utilized first. In this way a variety of cross-shunting of axons is introduced which is attributable solely to variations in the size of the endoneurial tubes. Many of the fibre pathways recreated in this way would certainly bear no relationship to the original fibre pattern. The wasteful regeneration arising as the result of two or more axons finding their way into the one tube is less likely to occur, however, when the tubes are small and able to admit only one process. For this reason the multiple filling of a single tube is more likely to be excessive when repair is executed at a time before the tubes have atrophied unduly.

(C) *The number of fibres representing individual branches.*—In view of the competition of regenerating axons for endoneurial tubes the number of nerve fibres representing individual branches at the suture level has an important bearing on the effectiveness of regeneration. If the fibres of a particular branch are numerous, there is more chance of some of their regenerating axons reaching corresponding endoneurial tubes; a contributing factor in this regard is the multiple budding of axon sprouts which occurs during regeneration. When, on the other hand, the fibres to a branch are few in number, their chances of establishing correct continuity when competing for endoneurial tubes will be correspondingly reduced. Information relating to the cross-sectional area of peripheral nerves occupied by the fibres representing individual branches is available (Sunderland and Bedbrook, 1949).

(4) *Factors which Affect the Conversion of the Restored Pathway into an Efficient Fibre System*

It has been claimed that localized constriction "deprives that part of a regenerating fibre lying beyond it of some factor essential for its further growth in width and myelinization" (Weiss and Taylor, 1944*a*). Scarring at the suture line may, by constricting the regenerating axons in the initial stages of their growth, restrict maturation processes upon which the efficient functioning of the fibre depends.

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(5) *The Loss of Branches in the Vicinity of the Injury Owing Either to Direct Damage or to the Avulsion of the Branch Fibres from the Nerve Trunk or Muscle*

The manner in which this complication adversely affects recovery requires no elaboration.

(6) *General Conclusions*

The overlap of funiculi which occurs as the result of (i) dissimilarities in the funicular patterns of the nerve ends, (ii) the extent of the separation of the funiculi, and (iii) the atrophy of those below the lesion, leads to the loss of large numbers of axons into the interfunicular spaces of the distal stump. In this way the factors responsible for the overlap, which operate in every case but to a variable degree, constitute a serious threat to recovery.

A large number of factors also combines to prevent regenerating axons from entering endoneurial tubes originally occupied by them. This complicates regeneration in two ways: (i) by adding to the loss of axons which is the fate of those entering morphologically unrelated tubes (e.g. motor axons into sensory tubes and vice versa) and (ii) by confusing the original pattern of innervation. The axon mixing which occurs at the suture line does not, however, affect all branch fibre systems to the same degree. Where the fibres representing individual branches are partly or sharply localized in the nerve trunk, such a localization will, providing correct funicular relations can be maintained during repair, assist the restoration of useful connexions. In addition, the more regenerating fibres which correspond to a particular structure the greater are the chances of recovery in that structure. Conditions are, therefore, more favourable for recovery in those systems in which the fibres representing the branches are numerically greatest and are sharply localized in the nerve at the site of repair. It is for this reason that, after repair in the proximal part of the limb, the axons for the proximally innervated structures have a distinct advantage over those running to distal regions.

Finally factors operating in the bridging tissue may lead to a constriction of the new axons which adversely affects conduction along them.

These factors are never absent though they operate to a variable degree from case to case. Each creates conditions which combine to prevent the restoration of useful pathways and in this way to neutralize the powerful and persistent efforts which neurons make to send new processes to the periphery. They are particularly destructive to recovery because, with few exceptions, the conditions introduced by them defy correction. One exception concerns the atrophy of the funiculi in the distal stump. This increases progressively for the first four months of denervation after which the conditions remain substantially the same. From this it follows that the chances of axons reaching the funiculi diminish progressively over this period which is an argument in favour

of repairing the nerve with as little delay as possible. Another exception concerns those factors which are responsible for the formation of a bridging tissue which adversely affects the movement of axons in a direction favouring the restoration of useful connexions and which later constricts them. The influence of these factors can be reduced by employing a suture technique which does not excite or aggravate the formation of an unfavourable junctional tissue. The practicability of undertaking funicular suture in order to reduce the adverse effects introduced by the erroneous cross-shunting of some axons and the loss of others is being investigated.

IV. Factors Operating in the Peripheral Pathway Below the Lesion

Factors operating in the peripheral pathway below the lesion may influence the course of regeneration and the quality of the recovery by affecting (i) the descent of the axons and (ii) the conversion of the restored pathway into a functionally efficient fibre system.

(1) *Factors Affecting the Descent of the Regenerating Axons along the Endoneurial Tubes*

Normally the products of degeneration have been removed and the macrophages have departed by 90 days. On occasions, however, both debris and cells may persist in a form which not only restricts the proliferation and movement of Schwann cells but also obstructs the passage of advancing axons. In this way they may well become a permanent obstacle to the descent of some axons. The conditions under which this complication appears and the extent to which it operates in individual fibres are still undefined.

Reference has already been made to the shrinkage of the endoneurial tubes which occurs with degeneration. There is evidence that this tubal atrophy does not retard the descent of regenerating axons. Thus once axons have entered endoneurial tubes in the distal stump regeneration follows much the same course after periods of denervation of at least twelve months as after periods of short duration (Sunderland, 1949, 1950). Holmes and Young (1942) have also shown experimentally that "once within a peripheral stump which has been degenerated for a long time, however, fibres may proceed as rapidly as into a freshly cut one."

(2) *Factors Affecting the Conversion of the Restored Pathway into a Functionally Efficient Fibre System*

The maturation of the new axonal pathway, on which depends the restoration of its functional efficiency, involves such processes as myelination and the restoration of the calibre of the fibre. Consequently any factor which restricts these processes should permanently impair the function of the fibre. The influence of endoneurial tube size on the restoration of the diameter of the regenerating fibre has been the subject of considerable experimental investigation (Holmes and Young, 1942;

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Sanders and Young, 1944; Simpson and Young, 1945; Hammond and Hinsey, 1945). In these studies it was suggested that "very small Schwann tubes in the peripheral stump have a restrictive influence on fibre growth" and that the denervation shrinkage, which increases rapidly with the period of denervation, soon results in a reduction of the lumen, so that the regenerating axons which reinnervate tubes smaller than those originally occupied by them remain of reduced size. This it is claimed results in the permanent impairment of the conducting properties of those fibres which fail to reach their original diameters. As a result of further investigation, however, Sanders and Young (1946) have shown that "connexion with the periphery is, therefore, able to produce an increase in fibre diameter which overrides any constriction of fibre growth produced by the slightly smaller Schwann tubes." Apparently, however, these workers do not include, in the category "slightly smaller Schwann tubes" the very small tubes to which they had previously attributed restrictive influences on fibre growth. Whether or not a tube will exert a restrictive influence, therefore, hinges on the definition of the terms "slightly smaller" and "very small." In the absence of any clear distinction between the two, the inference is that tubes not exceeding 3 μ in diameter would adversely affect the restoration of the original diameters of the large fibres.

Recent work has emphasized the considerable endoneurial tube atrophy which follows the continued denervation of the distal stump, an atrophy which rarely leaves a tube greater than 3 μ in diameter after three months' denervation (Sunderland and Bradley, 1950*b*). The question to be decided is whether or not this atrophy is irreversible for, if it is, nerve repair undertaken later than three months after severance must result in permanent immaturity of many of the regenerated fibres and, consequently, in a severe residual functional disability. However, a study of the course of regeneration and a precise evaluation of the end-results after delayed repair in human patients have revealed that the distal stump retains the capacity for at least twelve months of transmitting axons to the periphery in a manner that does not differ significantly from that observed when repair is undertaken immediately or shortly after severance and that muscle function can be fully restored following reinnervation when the distal stump has been denervated for the same period (Sunderland, 1949, 1950).

From this it appears that the endoneurial tube atrophy does not prevent those changes in the restored axonal pathways which convert them into functionally efficient pathways. The precise morphological nature of the changes occurring in regenerated fibres in human nerves under these conditions remains unknown. If it represents the restoration of original fibre diameters, then, regardless of animal experiments to the contrary, the endoneurial tube shrinkage, which is maximal and severe by the third month, must be reversible. There is, however, some experimental evidence (Weiss, 1941; Alexander, Woods and Weiss, 1948; Duncan,

1948; Sunderland, 1951) to suggest that it may not be necessary for the recovery of muscle function that the nerve fibres should be restored to their original diameters but that it could be due to regenerated pathways regarded in the customary sense as morphologically immature.

(3) *General Conclusions*

There is no form of therapy which influences the changes which develop in the peripheral segment following denervation. However, though the point at which the denervation atrophy of the tubes adversely affects recovery is not known, there is evidence to indicate that it does not assume significance within the first twelve months of denervation.

V. Factors Operating in the Tissues Innervated by the Severed Nerve

The changes occurring in denervated tissues which affect recovery are those which (i) lead to a reduction in the number of its component units, (ii) prevent the effective reinnervation of the tissues by the axons which reach them, and (iii) reduce the efficiency of the surviving units after they have been reinnervated.

The changes which develop in a muscle which has been deprived of its nerve supply and the manner in which these affect the quality of the motor recovery following reinnervation have been investigated in some detail (Gutmann and Young, 1944; Bowden and Gutmann, 1944; Gutman, 1948; Sunderland and Ray, 1950; Sunderland, 1950). However, little that is relevant to the present discussion is known about the coincident changes which develop in the cutaneous tissues and the manner in which these modify sensory recovery. For this reason a consideration of the latter will be omitted from this paper.

A consideration of the restrictions imposed on recovery by extra-neural injuries does not fall within the scope of this paper. However, it should be noted that any such injuries may limit recovery in the field of the involved nerve following satisfactory regeneration. Unfavourable end-results after delayed repair may also be due to, or aggravated by, neglect of the peripheral tissues prior and subsequent to repair which encourages those irreversible changes in the peripheral motor mechanism that are prejudicial to recovery. It should not, therefore, be surprising if, in the face of such complications, repair ends in failure regardless of the number of axons that regenerate, reach their destination and maturate into efficient pathways.

(1) *Factors Operating Within Muscle*

(A) *Factors which lead to a reduction in the number of muscle fibres.*—From the biopsy examination of denervated human muscle Bowden and Gutmann (1944) found that "few, if any, muscle fibres have undergone complete disintegration after three years' denervation" but that "from three years onwards the possibility of any useful recovery is in question."

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This estimate of the survival time of denervated muscle greatly exceeds that reported in the experimental study of Gutmann and Young (1944) and Gutmann (1948). Recent observations (Sunderland and Ray, 1950) have shown, however, that striated muscles survive denervation for at least 485 days in a grossly atrophied but histologically recognizable form. Over this period degeneration and fibrous tissue transformation of fibres were rarely seen. Despite the gross muscle fibre atrophy and the connective tissue reaction which resulted in a thickening of the perimysium and endomysium, particularly the former, there was no disorganization of the architecture of the muscle.

Thus the loss of muscle fibres by degeneration and fibrous tissue transformation before they are reinnervated does not reach significant proportions within the period covered by the experimental and the clinical enquiries, namely 1·3 and 3 years respectively. In the experimental investigation (Sunderland and Ray, 1950) the animals were allowed the full freedom of a large cage so that their normal activities were unrestricted. As a result the affected muscles were subjected to passive movements throughout the period of denervation in that they were stretched and relaxed by unimpaired movements. It is conceivable that prolonged immobilization, in either a stretched or relaxed position, might give a different picture and this possibility is being investigated.

(B) *Factors which lead to a reduction in the number of reinnervated muscle fibres.*—Appropriate axons may fail to re-establish continuity with their old end-organs and may be unable to induce the formation of new ones owing to changes, such as fibrosis, which have developed as a result of the denervation. Some muscle fibres are therefore never reinnervated. According to Gutmann and Young (1944) "The proportion of old plates which is reinnervated falls rapidly as atrophy proceeds" while there is an increasing difficulty and slowness in the formation of new plates with increasing periods of denervation.

(C) *Factors which lead to a reduction in the efficiency of reinnervated muscle fibres.*—These comprise:

(*a*) the incomplete maturation of the new pathway consequent on atrophic changes developing in the denervated muscle. The calibre of the nerve fibre is only restored when the growing axon re-establishes continuity with its original or a functionally corresponding end-organ which suggests that the establishment of suitable terminal connexions influences the maturation of the fibre (Weiss, Edds and Cavanaugh, 1945; Aitken, Sharman and Young, 1947).

It would be of interest to know whether or not atrophied tissues retard or prevent the full maturation of the axons which establish connexion with them and, if they do, the point at which this influence significantly disturbs the restoration of function. According to Aitken, Sharman and Young (1947) the maturation of nerve fibres in rabbit material "is as rapid when they become united with muscles allowed to

atrophy for 100 or 140 days as when they grow directly into freshly denervated muscles. . . . Presumably with periods of atrophy longer than 150 days some decline in this power will become evident as the muscle fibres degenerate and disappear (Gutmann and Young, 1944)." An investigation of the capacity of human muscles to function efficiently following reinnervation has revealed that complete or very good restoration of function can occur following periods of denervation of at least twelve months (Sunderland, 1950). From this it is concluded that within this period either the maturation of the nerve fibres is not hindered or their failure to recover their original diameters is of little if any significance.

(*b*) the formation of new end-organs by axons which fail to re-connect with the old end-organs. Such new end-organs are probably less efficient than the old.

(*c*) the failure of the satisfactorily reinnervated muscle fibre to recover fully owing to changes developing within the fibre itself as the result of the denervation. The beneficial effects attributed to the electrical treatment of paralysed muscles may be due to an influence which this treatment has on the denervated fibre.

(*d*) intramuscular changes such as fibrosis which impair the co-ordinated activity of groups of muscle fibres either mechanically or by other means.

(2) *The Significance of the Muscular Changes in Limiting the Quality of the Recovery*

It next becomes necessary to examine the extent to which the morphological considerations outlined in the preceding sections are responsible for reducing the quality of the recovery. In doing so it is important to remember that assessments of the effectiveness of reinnervation after varying periods of atrophy should be based on the measurement of the functional recovery and not on the altered morphology of the tissues. Furthermore it is also to be noted that animal experiments deprive the investigator of the opportunity of measuring the functional response to voluntary effort which is the critical test of the effectiveness of reinnervation and the principal objective, on the motor side, of the repair of severed nerves.

Experimental investigations have given an exceedingly clear picture of the complexities of reinnervation processes and the manner in which the restored pattern becomes progressively more distorted as the period of denervation increases until ultimately it falls far short, morphologically, of the normal arrangement (Gutmann and Young, 1944; Gutmann, 1948). Nevertheless, in the absence of any suitable test of the response to voluntary effort in the experimental animal, the restrictions which are imposed on the restoration of function by these abnormal morphological changes must remain purely inferential. Patterns of reinnervation which

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appear abnormal histologically (excluding, of course, absence of reinnervation) may still be compatible with recovery of a useful degree. Because of these limitations it becomes necessary to have precise information relating to the quality of the voluntary motor recovery which follows the reinnervation of human muscles after prolonged denervation.

It has been shown recently that very good, and in some cases complete, restoration of function can occur in reinnervated human muscles following periods of denervation of up to twelve months provided that the quiescent muscle has been maintained in the best possible condition by appropriate therapy (Sunderland, 1950). This indicates that axons have been directed in sufficient numbers to their original, or functionally similar, end-organs and that the muscle fibres have responded to the reinnervation. From this it is concluded that the denervation changes in the muscle are reversible within the first twelve months of denervation. Though there is much clinical information to the effect that reinnervated human muscles are capable of contracting voluntarily after having been denervated for much longer periods, references to this recovery are not sufficiently precise to throw light on the maximum period of denervation which is compatible with good functional recovery.

The possibility remains, however, that intramuscular factors may be responsible for the residual paresis in those muscles which fail to recover completely after prolonged denervation. After nerve suture in the upper part of the limb, it is the proximally innervated muscles which recover completely or nearly so while the distal muscles show a poor recovery. This has been attributed by some to the longer period for which the latter have been denervated though no evidence has been advanced in support of these claims. Such an explanation is open to question. In the first place the quality of the recovery in the distal muscles after immediate or early suture is still inferior to that recorded for the proximal muscles after delayed repair despite the fact that the former have often been denervated for much shorter periods than the latter. Secondly other factors are operating which lead to poorer recoveries at the periphery of the limb. Briefly, conditions are more favourable for recovery in the proximal than in the distal muscles for the following reasons:

(i) In proximal injuries the neurons innervating the distal segment of the limb are the most severely affected by retrograde disturbances.

(ii) The nerve fibres supplying the proximal muscles occupy a greater cross-sectional area of the nerve (Sunderland and Bedbrook, 1949) and are more sharply localized at proximal levels than the fibres destined for structures further distally (Sunderland, 1945*b*; Sunderland and Ray, 1948). Thus in the competition for endoneurial tubes after high repair the axons for the distal muscles suffer a distinct disadvantage.

(iii) The consequences of loss of axons and disorderly reinnervation are more serious for the distal muscles than the proximal. The latter often combine as prime movers in executing movements and for this reason the reinnervation of one member of the group by fibres originally

supplying another does not seriously disturb the pattern. This assists in the restoration of function. On the other hand the muscles controlling the digits function as independent but well-integrated and co-ordinated systems in every movement, combining to give that delicacy, refinement and precision of action which, in the case of the hand, is the basis of manual dexterity. In these complex and finely adjusted movement patterns each muscle has a specific role to play. Consequently any disturbance of the fibre pattern during the regeneration of axons to these muscles seriously impairs the restoration of function.

It is stressed that the foregoing remarks have reference only to muscles which have been maintained in good condition by appropriate therapy. It is to be clearly understood that neglect of the peripheral mechanism in the form of permanent immobilization of the parts and exposure to cold leads to deformities, and, by encouraging vascular and lymphatic stasis within the muscle, promotes the degeneration of fibres and the development of fibrosis which seriously restricts recovery when reinnervation occurs. There is no doubt that the texture of human muscles neglected in this way is changed and that, other things being equal, the quality of the recovery in them is inferior to that occurring when the muscles have been suitably treated.

(3) *General Conclusions*

The complete or very good recovery after prolonged denervation in some muscles, together with the explanation advanced to account for the poor recovery in muscles innervated in the distal part of the limb, make it unlikely that intramuscular factors which are introduced by the denervation are responsible for the residual defect in those muscles which fail to recover completely.

The most potent factors responsible for the incomplete recovery are those which lead to:

(i) a reduction in the number of axons which reach the muscle as the result of retrograde neuronal degeneration together with the failure of others to reach endoneurial tubes in the distal stump. This means that many muscle fibres are never reinnervated.

(ii) the distortion of the pattern of innervation which results from the loss of some axons and the erroneous cross-shunting of others at the suture line.

(iii) a reduction in the efficiency of the restored pathway which in turn may be due to (*a*) persistent neuronal defects; (*b*) the overloading of neurons as a result of the branching of their regenerating axons which ultimately reinnervate a larger field than that originally served by the neurons. These additional pathways may make additional demands on the neurons so that they are unable to direct the normal functioning of the original mass of tissue supplied. The significance of this factor, however, remains obscure; (*c*) arrested maturation—investigations have shown that this cannot be attributed to either endoneurial tube shrinkage in the distal stump or muscle atrophy.

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The evidence suggests that changes developing within the muscle which are directly attributable to the denervation do not assume significance within the first twelve months of denervation: the changes concerned would be those reducing the chances of restoring useful neuromuscular connexions or producing a condition in individual muscle fibres which is incompatible with normal function after satisfactory reinnervation. The observations on which this conclusion is based were, however, made on denervated muscles which were exercised regularly and maintained in good condition by physiotherapy. It is emphasized that the development of unfavourable conditions within the muscle, in the form of fibre degeneration and fibrosis, are introduced and become a serious factor limiting recovery when the denervated peripheral mechanism is immobilized, exposed to cold and is deprived of those physiotherapeutic manœuvres designed to encourage the circulation and to exercise the denervated muscle fibres. This factor should never be underestimated in the treatment of any case. By adopting measures to prevent the development of these complications the surgeon takes advantage of one of the few ways available to him of improving the quality of the recovery.

VI. The Influence of the Level of the Suture on the Quality of the Recovery

Etzold (1881), Lehmann (1921) and Foerster (1929) noted that high repair was associated with a generally poorer result than low repair, while Stopford (1920) believed that "the prognosis was more favourable the nearer the suture is to the spinal cord."

A detailed analysis of the end-results in a series of cases of peripheral nerve suture (Sunderland, 1949) has shown that after high repairs the distal muscles can be expected to recover less frequently and, when they do, to a lesser degree than the proximal. The reasons for the more favourable recovery in the proximal than in the distal muscles have already been listed.

The quality of the sensory recovery in the hand following high repairs is also not as good as that following repairs at the wrist. This is so because at proximal levels the sensory fibres are scattered and thoroughly mixed with motor fibres, while at the wrist the fibres for individual cutaneous nerves are so well localized that the entry of regenerating cutaneous axons into corresponding or closely related endoneurial tubes is greatly favoured. Thus at the wrist, 94 per cent of the funicular cross-sectional area of the median nerves is occupied by sensory fibres and 6 per cent by the fibres for the thenar muscles, while the fibres for the various terminal branches are well localized in separate funiculi or groups of funiculi. Above the elbow, however, the terminal sensory fibres occupy 66 per cent of the funicular cross-sectional area of the nerve and the terminal motor 4 per cent; here, however, the fibres from the different terminal branches are now intermingled and are widely dispersed over the component

funiculi. Similar conditions obtain in the case of the ulnar nerve, where the values for the sensory and motor components (for the hand) at the wrist are approximately 56 per cent and 44 per cent respectively, while the corresponding values above the elbow are 35 per cent and 28 per cent. At levels in the forearm and leg where no localization of branch fibres obtains, recovery will, other things being equal, favour structures innervated by branches whose fibres occupy the greater cross-sectional area of the nerve.

VII. The Influence of the Interval between Severance and Suture on the Quality of the Recovery

The overwhelming superiority of immediate and early secondary repair has been convincingly established. Though there is no justification for the delay of suture beyond the time when it can be performed, it is, nevertheless, important to know the effect of the interval between injury and repair on the extent and quality of the recovery for the following two reasons:

(i) Awaiting signs of spontaneous recovery in lesions in continuity involves delays of up to six to nine months (Sunderland, 1947*b*). Do such delays adversely affect the end-result if resection and suture are ultimately required?

(ii) Considerable delays in the repair of severed nerves are often inevitable owing to, *inter alia*, gross injury to neighbouring parts and prolonged and severe infection. After what delays are attempts at repair no longer worth while?

Most writers have expressed the belief that the result deteriorates with increasing periods of denervation, though this opinion is based on the observation that, in any given series of cases, the number of successful results after early repair will far exceed that after late repair. This is unquestionably the case, but it is misleading to fix the point at which the delay is responsible for a significant deterioration in the end-result solely on the basis of a higher incidence of good recoveries after early suture when other factors that are known to influence the end-result have not been and cannot be excluded. It should not be forgotten that late repair is often imposed by conditions which considerably increase the hazards of repair, for example, more severe injuries with much destruction of tissue, prolonged and severe infection, and the presence of large defects in the nerve. Unfavourable end-results under such adverse conditions should not be surprising. The significant observation which appears repeatedly in the literature is that exceptional recoveries do follow repair that is delayed for considerable periods (Björkesten, 1947; Sunderland, 1949, 1950).

Despite the generally accepted belief that the result deteriorates with an increasing interval between injury and repair, little information is available as regards the point at which this deterioration becomes significant. It may be inferred from the clinical findings of Björkesten

(1947) that they assume significance "during the last quarter of the first year," while the experimental investigations of Holmes and Young (1942) indicate that delays "especially those greater than five or six months, produce conditions which at least are liable to retard recovery and may permanently prevent its completion." On the other hand, Stopford (1920) states that, excluding cases with widespread intraneural changes, "a delay of twelve to eighteen months appears to have no marked effect upon the date or extent of the recovery." More recently (Sunderland, 1949, 1950) it has been shown that repairs undertaken after delays of from six to eleven months may be followed by very good recoveries, which are equally as good or better than those following immediate or early secondary suture. Furthermore, in this group the course of regeneration, from onset to termination, did not differ significantly from that recorded after early repair.

Though the data in the clinical literature do not permit the establishment of a time limit beyond which repair would be useless, the work of Bowden and Gutmann (1944) on the biopsy examination of denervated human muscle indicates that irreversible changes, which are incompatible with recovery, are evident at three years.

(1) *The Effect of Time on the Factors Operating Proximal to the Lesion*

We have seen that the capacity of some surviving cells to provide new and functionally efficient pathways persists unimpaired for at least twelve months after they have been isolated from their peripheral connexions (Sunderland, 1950). Whether this capacity persists indefinitely remains unanswered.

It would be interesting to know if the early entry of regenerating axons into the endoneurial tubes in the distal stump exerts any influence on the survival and well-being of the neurons which control them. Though clinical and experimental studies have demonstrated the capacity of axons to sprout from the proximal stump of a severed nerve after long periods this cannot be accepted as proof that delayed regeneration has not resulted in a further reduction in the number of neurons surviving from the original injury. Furthermore, the occurrence of excellent recoveries after delayed repair may be due in some measure to compensatory mechanisms which would obscure an assessment of the total neuronal loss. A study of the retrograde changes following amputation of a limb suggests that the greater neuronal loss which occurs in these cases is due to the fact that effective regeneration cannot occur under these conditions. If this should be the case the further possibility exists that the number of cells which survive severance of a nerve may progressively diminish, if, for any reason, regenerating axons are unable to find the distal stump. However, one feels from an analysis of the clinical material that, within twelve months at least, delays in the

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performance of end-to-end suture do not add to the retrograde neuronal loss sustained as a result of the original injury.

Since multiple axonal budding could conceivably be an important factor in reducing the effects of the loss of axons in the proximal stump, or alternatively of adding to it, it would be important to know whether or not the capacity to bud in this way diminishes with time.

(2) *The Effect of Time on the Factors Operating at the Level of the Suture*

(A) *The quality of the bridging tissue between the nerve ends.*—Schwann cell activity at the nerve ends, upon which union and the success of regeneration are believed largely to depend, was found by Abercrombie and Johnson (1942) to be maximal in the rabbit between the 19th and 25th days after severance. Others, however, have reported maximal activity within the first week in the rat (Rexed, 1942; Hyden and Rexed, 1943; Holmgren and Rexed, 1947).

It is not possible to gauge the influence of this factor on the repair of human nerves since all the information required to permit an assessment of the relative influence of each of the several factors affecting the extent and quality of regeneration in the individual lesions is never available. However, direct inspection of the suture site some time after union (e.g. when a nerve was re-exposed at a later date), together with an examination of the course of regeneration and the quality of the end-result following repairs within and outside the period of maximum Schwann cell activity in the rat and rabbit, indicates that in human nerves Schwann cells retain the capacity to bring about effective union for very long periods (Sunderland, 1949).

(B) *The cross-sectional area of the distal stump and its contained funiculi which are available to the regenerating axons.*—Reference has already been made to the shrinkage of the distal stump which accompanies the atrophy of its component funiculi. Attention has also been directed to the manner in which the process is influenced by two factors: (i) the duration of denervation, and (ii) the variations in the relative amounts of the funiculi and epineurium comprising the nerve. Given a constant funicular pattern the atrophy of the distal stump increases progressively with the duration of denervation until the fourth month after which there is no further significant change. As a result of the variations in the funicular/epineurial ratio the atrophy of the distal stump shows irregular fluctuations, being greater when the nerve at the site of repair is composed of tightly packed funiculi than where the funiculi occupy a smaller cross-sectional area of the nerve. Regardless of the behaviour of the distal stump, the progressive atrophy of the funiculi means that the funicular area which is available for the regenerating axons is reduced while any funicular overlap resulting from a dissimilarity of the funicular patterns of the nerve ends will be accentuated. This means that the chances of regenerating axons going astray are greatly increased. On the basis of the foregoing

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observations there is good reason for believing that the chances of restoring useful connexions with the distal stump diminish progressively for the first four months of denervation, after which the conditions remain substantially the same.

The funicular shrinkage has an additional effect on regeneration. By leading to a concentration of the endoneurial tubes, the latter would have fewer axons reaching them than would otherwise be the case. Axon branching may offset this to some extent but in any event the arrangement is one which will add to the confusion of the fibre pattern.

Therefore, so far as these two morphological features are concerned, the first four months of denervation represent a critical period in regeneration in that at the end of this time the atrophic changes in the distal stump which threaten the restoration of useful connexions are maximal.

(3) *The Effect of Time on Factors Operating in the Peripheral Pathway below the Lesion*

Following severance of a nerve, the section below the level of the injury undergoes a series of characteristic changes the essential features of which are the proliferation of Schwann cells, the degeneration and removal of the axon and its myelin sheath and the conversion of the fibre encircled by the endoneurium into a Schwann band, Schwann tube or endoneurial tube. Reference has already been made to the atrophy of this tube with increasing periods of denervation. This residual tissue provides the best medium for the growth and passage of the regenerating axons to the periphery and for their subsequent maturation into efficient pathways. It is generally recognized, however, that the distal stump does not retain these desirable properties indefinitely but that a stage is reached when they decline with increasing periods of denervation until ultimately the development of irreversible changes converts the distal stump into a strand of tissue which is of little assistance to the regenerating axons. The point at which the changes become irreversible, however, is not known but there is evidence that it does not fall within the first twelve months of denervation for human nerves (Sunderland, 1949, 1950).

(4) *The Effect of Time on Factors Operating within Muscle*

It is generally recognized that denervation of tissues ultimately leads to a condition which is incompatible with the restoration of useful function when the tissue has been satisfactorily reinnervated. An upper limit, however, has not yet been fixed for the point at which the changes become irreversible. Complete or very good recovery can occur in reinnervated human muscles following periods of denervation of up to twelve months provided that the quiescent muscles have been maintained in good condition by appropriate therapy (Sunderland, 1950). From this it is concluded that the changes which develop in muscles as the result of denervation are reversible within the first twelve months of denervation. It is known that reinnervated human muscles are capable of contracting voluntarily after denervation for much greater periods. However,

references to this recovery in the literature are not sufficiently precise to indicate the point at which the changes occurring within the muscle as a result of the denervation become irreversible and of such a nature that they contribute significantly to the residual disability.

VIII. Compensatory Mechanisms

Few compensatory mechanisms are available to offset the influence of those factors which adversely affect the extent and quality of the recovery after nerve suture.

(1) *Compensatory Mechanisms Operating Proximal to the Lesion*

(A) *Axon sprouting.*—The degeneration of some neurons and the persistence of severe defects in others reduce the potentialities of the central mechanism for reproducing new axons. This loss may be offset to some extent by the multiple budding of the axons of surviving cells but the extent to which this operates in a useful way is questionable. It is possible that indiscriminate budding may adversely affect regeneration by aggravating the cross-shunting of axons at the suture line which leads them into foreign endoneurial tubes. Furthermore there is the added possibility that multiple budding may lead to a dissipation of the energies of the neuron over several pathways with the result that the cell is unable to direct the normal regeneration of any one of them. The status of multiple budding in aiding or restricting regeneration remains undefined as do those factors which influence the extent to which this morphological feature operates. Whether or not neurons undergo a compensatory hypertrophy in order to extend their control over a greater peripheral field is also not known.

(B) *Central adjustments.*—Reorganization of patterns of activity at central levels may compensate to some extent for the disturbances which are produced by the degeneration of neurons and by the loss of regenerating axons and the erroneous cross-shunting of others at the suture line. The range, however, within which such central reorganization is possible is limited (Sperry, 1945).

(2) *Compensatory Mechanisms Operating at the Suture Line*

Whether or not the tissues of the distal stump exert an attractive influence on the regenerating axons, thereby causing them to converge upon the funiculi, is still unsettled. Such an influence would reduce the loss occasioned by axons descending outside the distal stump but the observations reported by Weiss and Taylor (1944*b*) suggest that this does not occur.

(3) *Compensatory Mechanisms Operating at the Periphery*

The loss of some muscle fibres and the reduced efficiency of others may be offset by the "use" hypertrophy of those fibres which have fully recovered. The ingrowth of nerve terminals from adjacent intact nerve fibres to innervate denervated muscle fibres such as has been described

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after partial denervation of muscles (Hines, Wehrmacher and Thompson, 1945; Van Harreveld, 1945; Weiss and Edds, 1945; Edds, 1949; Hoffman, 1950) does not, of course, operate after the severance and repair of peripheral nerve trunks. It has been claimed, however, that an ingrowth of sensory terminals from adjacent intact cutaneous nerves occurs and reduces the area of the sensory disturbance which follows severance of a peripheral nerve (Weddell, Guttmann and Gutmann, 1941; Livingston, 1947).

IX. General Conclusions

It is apparent from this review that the course of regeneration after nerve suture is complicated by a large number of variables which operate at all levels along the pathway from the neuron to the tissue innervated by it. Recent investigations, in addition to emphasizing their importance, have added to their number and no doubt there are others which are still unrecognized. Furthermore, of the several variables that have been identified, the extent and severity of the effect exerted by some defy assessment while the full scope of the influence exerted by others has yet to be revealed. It is, consequently, impossible to determine the extent to which each of the participating variables contributes to the residual disability after repair and since function is never completely restored over the entire field served by the nerve we are deprived of a direct method of isolating those factors that do not adversely affect recovery.

Though the complexity of the reparative process and the impossibility of isolating each variable and studying it separately prevents a precise evaluation of the relative importance of each in regeneration, an analysis of the available data indicates that some factors affect the course of regeneration and the quality of the recovery more seriously than others. The most potent appear to be those which result in (1) the loss of some regenerating axons, (2) the inefficient functioning of others which have re-established continuity with appropriate end-organs, and (3) distortion of the original pattern of innervation.

(1) Axons are lost as the result of:

(*a*) Retrograde neuronal degeneration.

(*b*) The failure of regenerating axons to reach the endoneurial tubes in the distal stump. This is due to their entry into the interfunicular tissue or their failure to enter the distal stump owing to the atrophy of the latter and the presence of scar tissue which either blocks them or directs them elsewhere.

(*c*) The failure of regenerating axons to enter their original or functionally related endoneurial tubes.

(2) The inefficient functioning of restored pathways follows persistent neuronal defects, the incomplete maturation of the regenerated fibre and the distortion of the pattern of innervation.

(3) The original pattern of innervation is modified by the loss of some

nerve cells and nerve fibres and the erroneous cross-shunting of axons into foreign endoneurial tubes at the suture line.

Each of the above factors is in turn the product of, and is consequently influenced by, a host of other variables which have been identified and discussed in earlier sections.

The evidence suggests that changes occurring in the distal stump within the first twelve months of denervation do not delay or prevent the conversion of the restored pathway into an efficient fibre. It also indicates that, within the same period, denervated muscles retain the capacity to recover and function efficiently on reinnervation providing they are reached by regenerating axons in sufficient numbers and from appropriate centres. From this it is inferred that the changes developing within the muscle which are directly attributable to the denervation do not become irreversible within the first twelve months of denervation.

The observations on which this inference is based were, however, made on denervated muscles which were exercised regularly and maintained in good condition by physiotherapy. Clinical experience provides abundant evidence of the severe impairment of movement which follows prolonged immobilization and neglect of the denervated tissues. Such impairment, however, can hardly be directly attributed to the denervation. Nevertheless the readiness with which complications develop in the affected tissues, particularly in some patients who appear to show idiosyncrasies in this regard, emphasizes the importance of maintaining the parts in the best possible condition throughout the period of denervation.

Few compensatory mechanisms are available to offset the influence of those factors which combine to affect recovery adversely. The role of axon sprouting in this regard is of dubious value. Modification of the pattern of innervation which occurs during regeneration may be compensated by functional adjustments at central levels though this compensatory mechanism appears to operate in only a very limited way. Finally the compensatory hypertrophy of satisfactorily reinnervated muscle fibres offsets the loss of some units while the ingrowth of intact sensory fibres into denervated areas reduces the cutaneous sensory loss.

On the basis of the data recorded it is obvious why the prospects of nerve repair are so uncertain. Furthermore, because the factors which adversely affect recovery are, with few exceptions, beyond the reach of therapy and the skill of the surgeon, it is also apparent why the outlook for effecting improvements is particularly disheartening. However some encouragement is to be gained from the fact that the peripheral nervous system possesses tremendous recuperative powers. If these are to be assisted to achieve a useful result those factors which can be influenced by artificial measures should be distinguished from those which cannot because it is upon the former that efforts must be concentrated when repairing the nerve and when planning modifications of technique and treatment. Unfortunately these factors are few in number

and are completely overshadowed by those which are beyond control. However because they provide the only means of assisting regeneration they deserve the most careful consideration. The gentlest handling of the nerve and nerve ends during repair reduces the retrograde effects while the suture technique employed should be such as to prevent or minimize the development of unfavourable conditions in the junctional tissue which hinder regeneration and favour the loss of axons. The severed nerve should also be repaired with as little delay as possible because the funicular atrophy which prejudices the chances of the axons making useful connexions with the distal stump increases rapidly to reach a maximum value at the end of the fourth month after which there is no further significant change. The practicability of undertaking funicular suture in order to reduce the harmful effects of the erroneous cross-shunting of axons is being investigated.

The information provided is useful in two other ways. In the first place, if any reliability is to be claimed for prognosis it is essential that the latter should be based on a clear understanding of the factors which operate to affect recovery and the manner in which each exerts its influence. Secondly, it emphasizes the caution which should be exercised when attempting an evaluation of any modification of surgical technique or treatment. The results of such an enquiry will be inconclusive unless all the factors influencing the extent and quality of the recovery are considered. Additional emphasis is given to this point when it is remembered that it has not yet been possible to assign to some factors their relative importance in the repair process. However, the absence of essential information has not deterred some from assigning to the interpretations of their observations a finality that is unwarranted and misleading. This subject will assume considerable importance when the end-results of large numbers of nerve sutures from the Second World War are analysed to settle controversial issues relating to repair. From a study of past records it is evident that the interpretation of the end-results in terms of the nature of the injury and the conditions of suture has often been fallacious because investigators have been preoccupied with certain factors to the exclusion of others which are of greater significance.

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ALTERED CONSCIOUSNESS ASSOCIATED WITH BRAIN-STEM LESIONS

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THAT alterations of consciousness may arise from lesions of the brain-stem is not a new observation. Gordon Holmes (1904) in his monograph on tremor from disease of the red nucleus mentioned in passing that 2 of his patients showed increasing drowsiness for some weeks before death, and Kinnier Wilson (1920) in his discussion of decerebrate rigidity in man recognized that compression of the mid-brain was an effective cause of unconsciousness. In the early reports of epidemic encephalitis it was quickly established that the brunt of the disease fell, clinically and pathologically, upon the mid-brain, and it was held that damage in this region might contribute to the characteristic lethargy and stupor. In the last fifteen years or so, since the mechanism of the tentorial pressure cone came to be understood, the problem of disordered consciousness from brain-stem damage has attracted increasing attention, particularly from neurosurgeons. Penfield (1938) wrote that long-continued unconsciousness seemed to mean a lesion in an area somewhere above, but not far removed from, the mid-brain. He recorded that twice, after operations upon the posterior fossa, he had seen a stuporous condition result, eventually coming to resemble permanent sleep, in which the patient lived by the aid of tube feeding for several months. In 1944 Geoffrey Jefferson went a step further in analysis, and declared that derangements of consciousness (which he termed parasomnia, to bring out their essential relationship with sleep) in his experience arose not uncommonly from injury to the mid-brain, and in diminishing degree from pons and upper medulla. He postulated that there might be a waking centre, a circumscribed brain area, extending through these parts of the neuraxis, interference with whose function led to obscuration of consciousness. With R. T. Johnson (1950) he has reaffirmed his conviction with illustrative cases. In their study of the syndrome of occlusion of the basilar artery Kubik and Adams (1946) have drawn attention to disturbances of consciousness, ranging from slight confusion to deep coma, as one of the earliest and most constant features in the clinical picture, and a case of pontine hæmorrhage in which the dominant symptoms was persistent sleep, gradually deepening into profound coma and ultimate death, has lately been recounted by Purdon Martin (1949). Martin speculated that the

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train of events witnessed in his patient were attributable to bilateral interruption of the lemniscal systems by the hæmorrhage.

It seems worth while to present in the following pages the histories of 6 patients, all of whom showed disturbances of consciousness, in conjunction with signs plainly indicative of mesencephalic disorder.

Case 1.—Irene S., aged 10. The third of four children. Birth normal. No relevant illnesses. Family history non-contributory. When she was 3 months old, went off to sleep in her cot, and later could not be roused. Admitted to hospital, where she remained comatose for a week before gradually recovering. Then perfectly well until she was 7. One morning in March 1948 was playing at home, and fell into a sleep from which she could hardly be waked. Admitted to hospital where, although semicomatose for three or four days, no abnormal physical signs were detected. Seven months later she had a similar attack, this time prefaced for half an hour (her mother says) by a complaint of frontal headache and vomiting before she lapsed into sleep "just as though proper tired." Readmitted to hospital, she was noticed to have a squint and pupillary inequality, the right pupil being smaller than the left. In a few days her conscious state returned to normal and the ocular signs disappeared. Early the next year, in February 1949, she had a fourth attack of lethargy and drowsiness, again with squint and pupillary inequality, and it was said that the optic discs were swollen. Her cerebrospinal fluid was normal. After four days she began to recover and was soon completely well. At the extreme end of April again passed swiftly into stupor, and, after admission to a local hospital, was transferred on May 1, 1949, to the Queen Elizabeth Hospital, Birmingham, under the care of Professor Brodie Hughes. On arrival she was semicomatose, and not sufficiently co-operative for thorough neurological examination. It was noted that the nasal margins of the discs were indistinct; the pupils small and equal, but the right not circular, and neither reacted to light: there was a divergent squint of the eyes which did not travel properly together, though each individually seemed to have a full range of movement. There were no other neurological signs, no neck stiffness or limitation of straight leg raising. General systemic examination was negative. Various investigations were made without disclosing abnormality (full blood-count, blood urea and blood sugar estimations, and skull X-rays). The C.S.F. pressure was 190 mm., but its chemistry and cytology were normal. By May 6 she appeared to have recovered perfectly, except that the right pupil was smaller than the left, and sluggish in its light reaction. Ventriculography at this stage showed some enlargement of the lateral and third ventricles. The iter could be seen, and the upper part of the fourth ventricle was well filled, but not dilated. Its lower part, however, could not be seen, and it was suspected that there might be a tumour in this region, causing intermittent obstruction of C.S.F. outflow. On May 19 posterior fossa craniotomy was made. The cerebellum and fourth ventricle appeared normal, and exploration of the vermis, which was deliberately split in its lower third to make sure it was not the seat of a tumour, was negative. Post-operative course uneventful. The child was sent home on June 2.

She was free of symptoms of any kind for just over a year. On July 27, 1950, she was readmitted into the charge of Professor Brodie Hughes in a further episode. She was very drowsy and continually yawning; she scarcely spoke and seemed quite uninterested in her surroundings. The right pupil was once more smaller than the left and eccentric, and both responded poorly to light. There was complete loss of conjugate upward movement of the eyes, and paralysis of abduction of the right eye. She seemed to have great difficulty in ocular convergence. There was slight weakness of the left side of the face and of the left limbs, which were also ataxic and hypotonic, and the left plantar was weakly extensor. Within a week her conscious level was normal, and her physical signs gradually subsided leaving only a persistent inequality of the pupils. Vertebral angiography and a further ventri-

culography were carried out, but proved of no great diagnostic value, though the latter showed once more a failure of filling of the lower part of the fourth ventricle. Because of this it was decided to re-explore the posterior fossa. Again no tumour was found, but on inspection of the brain-stem there seemed to be an unusually large number of venous channels overlying the corpora quadrigemina, much like those seen on the surface of the cord in spinal angiomata. A diagnosis of mesencephalic angioma was made, and the child sent home as soon as she had recovered fully from the operation.

Was well after this until January 15, 1951, when her mother says she was "practically a full week asleep" in the local hospital, and there was another relapse on March 25 for which she was also admitted to hospital. At Whitsun she again began to be sleepy but not so severely as usual, and this time was kept at home. She complained of the proper use having gone from her legs and was unable to stand without support. She could not use her arms to do anything, apparently because of ataxia. Her mother did not see anything wrong with her eyes except the pupils being of different sizes, as they had been ever since the summer of 1950. The child recovered in four days. When examined on May 29 there were no neurological signs beyond the disparity in pupil diameter, and sluggishness of the smaller (right) one in reacting to light and convergence.

Summary.—A girl now aged 10 with a history of nine attacks of pathological sleep, each of rapid onset and more gradual decline, lasting up to a week at a time. Initially they occurred without development of focal signs, but latterly have come to be associated with indications of disorder of function in the mesencephalic and upper pontine tegmentum, mainly on the right side. There are grounds for thinking that the causal lesion is an angioma.

Case 2.—Doreen C., aged 17½, a schoolgirl. Said to have been born with a fractured skull, and to have been concussed at age of 2. History of recurrent aural discharge (following pneumonia aged 5) until she was 12. Menarche at 14: periods always very irregular. Family history not significant.

In February 1949 she woke one morning to find the right eyelid drooping, so that she could not see properly out of the eye. This cleared up in a fortnight, to be succeeded a few days later by transitory and less marked left-sided ptosis. From this time onwards there was occasional drooping of both upper lids, not so pronounced as in the beginning, affecting right side always more severely than left. In October 1949 she sought medical advice, partly because there was now persistent right ptosis of variable degree, but mainly because she had begun to get frontal headache. Eventually admitted to Queen Elizabeth Hospital under the charge of Professor P. C. P. Cloake on January 15, 1950. On examination at this time there was bilateral ptosis, right worse than left, which varied in severity from day to day. No diplopia though there seemed at times to be a little weakness of upward movement of the left eye, and inconstant nystagmus on looking to the left was sometimes seen. Neurological examination otherwise negative. General examination also negative except for slight hirsuties and a persistent high blood pressure (170/110). Skull and chest X-ray normal. C.S.F. pressure and contents normal. C.S.F. and blood W.R. negative. EEG. normal. Full blood count normal. Urine examination normal. Urea concentration test normal. Urinary 17-ketosteroids within normal range.

Although two trial injections of prostigmine were without effect on the girl's ptosis, it was felt that the most probable diagnosis was myasthenia gravis. This diagnosis was soon ruled out by subsequent events. At the beginning of February she began to complain of occipital headache, commonly waking her from sleep in the early morning. On February 19 in the early afternoon she suddenly felt faint

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and after a few minutes collapsed unconscious. Examined at this time, she was quite unrousable, with fixed pupils, and profound and unyielding hypertonicity of all four limbs in extension with an opisthotonic arching of neck and back. She was completely unconscious for about an hour. On re-examination four hours later she was rousable with some difficulty and complaining of occipital headache. Neck flexion met resistance, and though her arms were no longer very stiff, her legs could be passively flexed only by the use of considerable force. Lumbar puncture was performed and gave a clear fluid under normal pressure which contained 10 cells (two-thirds polymorphs). Two days later she was still lethargic and drowsy. There was bilateral ptosis, right external rectus weakness, nystagmus to right and left, and marked plastic rigidity of the legs, with slight rigidity of the arms and neck. Pupils now reacting normally. Optic discs normal, no pyramidal or sensory signs. Lumbar puncture repeated: manometrics normal, protein 25 mg., globulin negative, cells less than 1, chlorides and sugar normal. She remained torpid for a week, during which she had to be catheterized several times. The extrapyramidal rigidity of her limbs gradually diminished, though it was still evident when she was discharged from hospital on April 22, 1950: the external rectus weakness and nystagmus, however, had gone, though ptosis remained as before. No definite diagnosis was arrived at, though the site of the lesion was plainly mesencephalic.

After returning home the stiffness of her limbs, of which she had been keenly aware subjectively and which had made her disinclined to use them, gradually waned. By the end of May she felt well enough to go for a day's outing. On the way back a dazed sleepy feeling gradually came over her, till she finally lost consciousness and had to be taken into hospital in a country town. She was somnolent for forty-eight hours, and her limbs were stiff subjectively for a week. Six weeks or so later, in July, at an evening service in church, a tired dazed sensation again seized her and after a while she lost consciousness briefly and had to be taken home. There was a return of stiffness in her limbs for two or three days, and of occipital headache. Two months later, on September 17, 1950, felt sleepy and tired all day and in the late afternoon developed occipital headache. At 8 p.m. collapsed unconscious; according to her mother her body and limbs were stiff and her face rigid for an hour. Readmitted the same night to the Queen Elizabeth Hospital under Professor Cloake. On arrival she was conscious but unable to speak, only uttering inarticulate sounds. There was bilateral ptosis and paralysis of external rotation of the right eye. Bilateral weakness of the face and defective movement of palate and tongue, all of supranuclear type. Some weakness of arms and legs with very marked rigidity of arms and especially of legs, without alteration of tendon reflexes or pathological change in the abdominal or plantar responses. Within an hour of admission her speech had returned, and the rigidity had decreased. She was only kept in hospital four days: she comments that she felt "dazy, sort of sleepy" all the time for the next week or more, but nevertheless went back to school when the term began. Throughout the Michaelmas term, was getting a lot of drooping of the eyelids, and fairly frequent occipital headache (which she describes as a dull ache with superimposed brief stabs of sharper pain). Missed last week of school because she was so tired and lethargic, and observed something the matter with her left hand for a few days, so that it would not move quickly or do things properly (as typewriting, which she was learning). In February 1951 she says she suddenly got very much better, her eyes not so droopy and no headache, and the improvement has so far been maintained. When examined on May 29 there was moderate right, and slight left, ptosis. Pupils not quite circular or central: right more eccentric and in dim light smaller than left. Both react to light, the left less promptly with hippus and gradual redilatation on continued illumination. Convergence response normal. Eye movements full, no diplopia, a little irregular nystagmus on looking to left. Slight plastic increase of

tone both arms, more marked in legs. Gait normal except that neither arm swings at all. Blood pressure 135/80.

There is still no direct clue to the pathology of this girl's condition. Its relatively long duration and remitting course suggest that neoplasm is unlikely, and there are no grounds for suspecting a luetic origin. The choice is seemingly between a recurrent demyelinating process and a series of small vascular accidents.

Summary.—A schoolgirl now aged 17½ who started two and a half years earlier with variable bilateral ptosis. After a year there was a sudden episode in which she lost consciousness for an hour; simultaneously she developed further ocular signs and marked rigidity (recalling the decerebrate state) of trunk and limbs, all indicating an upset at mesencephalic level. After this she remained torpid for a week. In subsequent months, had three essentially similar attacks, in one of which she was temporarily anarthric with other transient signs like pseudobulbar palsy: in each there was abnormal sleepiness of several days' duration. The nature of the causative lesion is not known.

Case 3.—Raymond W., aged 22, sheet metal worker. Nothing relevant in previous medical or family history.

While cycling on the afternoon of January 13, 1951, about 4.30 p.m., he began to suffer generalized headache and found that he could not see properly, which he attributed simply to failing daylight, but soon realized that it was in fact caused by drooping of his upper eyelids. He experienced difficulty in riding straight, and eventually fell off bicycle after running accidentally into the grass verge. When he tried to remount he discovered that he could not keep balance on his feet, and became conscious that he had severe double vision with wide separation of the images. Waited by roadside for his friends. When he spoke, his speech was "sticky-like and tongue-tied." He tried to walk with help, but found the right leg dragging. Admitted a few hours later under Professor P. C. P. Cloake at Queen Elizabeth Hospital. On arrival he was semicomatose but could be roused to give some account of himself. His speech was slurred. Bilateral ptosis of moderate degree. Pupils small and non-reacting. Complete absence of upward movement of the eyes, paralysis of abduction of left eye and weakness of abduction of right eye. Convergence very poor. Nystagmus with eyes at rest, exaggerated by movement. Right facial weakness of upper motor neurone type. Slight weakness of right arm and leg, with cerebellar ataxia of all four limbs (the right considerably more affected than the left); tendon reflexes diminished on right, right superficial abdominals depressed, and both plantars extensor, the right more strongly. Some disturbance of postural and vibration sense in right arm and leg. No neck stiffness or limitation of straight leg raising. Lumbar puncture gave a uniformly blood-stained C.S.F. under pressure of 280 mm. of water; C.S.F. analysis—30,650 red cells/cu.mm., protein 80 mg., globulin tests positive. Skull X-ray normal. Full blood count normal. Blood W.R. and Kahn negative.

He remained extremely somnolent for two or three days after admission and now has little or no memory of this period. For the next fortnight he felt perpetually sleepy and dropped off to sleep more or less whenever left alone. His physical signs gradually abated without changing their essential character. C.S.F. examination, repeated on January 26, contained no red cells, 14 white cells (93 per cent lymphocytes), protein 50 mg. and a trace of globulin: no xanthochromia. It was thought that the patient must have had a vascular lesion at mid-brain level, with

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subarachnoid leaking of blood, the underlying lesion being a congenital anomalous formation of the blood vessels, either angiomatous or aneurysmal. The question of vertebral angiography was debated: it was felt wisest to postpone this investigation until convalescence was further advanced. He was discharged, to rest in bed at home for another month, on February 20. Readmitted on April 12; abnormal physical signs subsided further: in particular could now look upwards. Cerebrospinal fluid pressure and composition normal. Two separate attempts at percutaneous vertebral angiography were unsuccessful.

Examined on May 28. Still complaining of constant diplopia though separation of images now only slight. He now notices little fault with right arm, but right leg drags after walking a mile or so, and he finds balance on right foot is not normal when he is dressing. Feels very well and has recently returned to full work. On examination: eye movements of full range, fine nystagmus to right, coarser to left; coarse nystagmus, especially of right eye, on looking downwards, finer and more rapid on looking up. Diplopia in all directions. Convergence full, but accompanied by jerky irregular nystagmus. Slight left ptosis. Outstretched right arm shows fine tremor, is rather easily displaced and there is definite rebound. There is intention tremor, mild dysdiadochokinesis and slight weakness of right hand and arm, and the deep reflexes are a trifle brisker than the left. A little depression of vibration sense at the right wrist. Both legs slightly ataxic, right worse than left, and right leg-jerks brisker than left with a weak extensor plantar response on the right. Vibration sense a little diminished bilaterally at ankles, right more than left. Ordinary gait looks virtually normal, but patient cannot walk heel-to-toe and shows a typical, though slight, cerebellar unsteadiness in turning. When he first takes stance with feet together, balance is obviously defective, though after a moment he can hold it without swaying and is not disturbed by closing his eyes.

Summary.—A young man of 22 who developed acutely signs and symptoms of mesencephalic derangement, namely fixed pupils, ptosis, external ocular palsies, nystagmus, bilateral pyramidal and cerebellar signs (both predominantly right-sided), some disturbance of postural and vibration sense in the right limbs and dysarthria, together with evidence of spontaneous subarachnoid bleeding. There was no complete loss of consciousness at any time, but he was pathologically somnolent for about three days, sleeping almost continuously, and lethargic for a further fortnight. There was gradual, but incomplete, recession of neurological signs. The exact nature of the causal lesion is unknown, but a congenital anomaly of blood vessels in the region of the upper brain-stem is suspected.

Case 4.—Alan T., aged 38, a sales engineer. Previous medical history not relevant. His younger brother died in 1944 at the age of 26 from a suddenly developing spontaneous subcortical hæmatoma, the exact source of which was not determined. One sister, six years older than himself, said to have had "recurrent hæmorrhages in her eye" for the last eight years.

On Christmas Eve 1950 was hanging decorations in his home, when his head suddenly felt funny in a way that he cannot exactly describe. His sight became confused as though looking through running water, and his legs felt painful especially in the calves. He sat down in a chair, and after a while was able to walk upstairs with help from his wife. By the time he got into bed there was severe headache, mainly occipital. Stayed in bed four days, complaining of intense pain in the back of head and neck, and scarcely slept. On December 29 admitted to a local hospital. No abnormal signs were discovered except those of meningeal irritation. A diagnosis of spontaneous subarachnoid hæmorrhage was made, but

lumbar puncture not done. Was well on the way to recovery when, on January 15, 1951, he moved his head sharply whilst washing his neck, and was seized with diplopia and a return of pain in the back of his head. Again no untoward signs other than neck stiffness and restriction of leg raising. No lumbar puncture. Three weeks later (February 6) he again complained of diplopia and occipital headache and shortly lost consciousness. Examined at this time his pupils were dilated and fixed, the right larger than the left. The deep reflexes were all increased, left more than right, with bilateral ankle clonus, the abdominals all absent and the plantars extensor. Some hours later, he was rousable but very drowsy. Left facial weakness was now noticeable, but otherwise there was no change. Twelve days later (February 18) he was still very drowsy, and the pupils still unequal but now responding slightly to light; there was divergent squint and very defective ocular convergence, bilateral nystagmus, and the fundi showed some swelling of the discs. The left side of the face was weak, the abdominals on this side absent and the plantar response upgoing. On February 26 he was admitted to the Queen Elizabeth Hospital under the care of Dr. Gilbert Hall, He was sleepy, disorientated in time and place, and amnesic for details of his illness. His speech was slurred and on one note, so that it was difficult to understand. Mild choking of both discs. Pupils equal but acting sluggishly to light. There was paralysis of conjugate upward deviation of the eyes, paralysis of adduction of the right eye and weakness of its abduction. Nystagmus was present in all directions of gaze. Slight left facial weakness of supranuclear type, left tendon-jerks brisker than right and left extensor plantar response. There was no neck rigidity or Kernig's sign. Lumbar puncture gave a C.S.F. pressure of 300 mm. water, with a protein content in the fluid of 30 mg., a trace of globulin, and 3 lymphocytes. Lange curve 0000000000. Skull and chest X-ray normal. Blood W.R. and Kahn negative. Full blood-count normal. In the course of the next fortnight there was slow improvement in his state. His physical signs indicated a mid-brain lesion and, in view of the pattern of his illness and the family history, a congenital vascular anomaly seemed its most likely cause. Vertebral angiography was therefore carried out on March 13: the films appeared to show unusual density of small vessel shadows in the upper brain-stem. Over the next three weeks the patient made rather rapid progress. His conscious level returned to normal, the disc swelling had quite gone and his other signs somewhat abated. He was allowed to go home on April 3.

Subsequent progress.—He was seen as an out-patient on May 30. He is now amnesic for everything that happened between February 6 and March 13, the day of the angiography. His chief complaints are diplopia on looking to left and difficulty in focusing his eyes. If he moves his head, or particularly if he tries to follow a moving object, it takes a definite while to pick up the focus, and needs conscious effort which he finds tiring. He says his left arm is not quite right. When he first went home he discovered that he tended to do everything with his right hand, although naturally left-handed, and was apt to hold his left arm stiff and motionless, bent at the elbow and rather out from his body "as though it was paralysed although it wasn't." The arm still does not relax properly, and his fingers do not work as fast or as accurately as they should. He is aware that his voice is monotonous in speaking, and if he sings he has difficulty in pitching his voice right. He is irritated by his dysarthria. He laughs a little more readily than he used to, and is upset that once he starts laughing it is very hard to stop. He cries easily too, "because he gets so sorry for himself." He says that his mental processes are no longer as swift or effortless as they were before his illness, and his memory less reliable. He complains of a "vague" feeling, which is with him all the time, as though he was doing things, even speaking, automatically, whilst himself a long way off. On examination there is a quasi-Parkinsonian economy of movement about him. He sits unusually still, blinks infrequently, and although his face is by no means expressionless, expression is slow in developing. In walking his posture

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is rigid and statuesque, and his left arm does not swing. His gait is a little slow but his stride not obviously shortened. Speech is a trifle slurred and his voice without range of tones. There is still almost complete failure of conjugate upward gaze, and the right eye does not quite reach the inner canthus on looking to the left. The left arm shows some slow regular tremor in maintained posture which is aggravated against resistance, and is a little jerky but not ataxic in movement. There is no weakness of the limb, but fine and alternating movements are slow as compared with the right. There is plastic increase of tone with inconstant cogwheel give. The tendon reflexes are slightly exalted. Tapping with the left foot is slowed, and the left leg-jerks are increased without palpable alteration of tone. The left plantar response is still doubtfully extensor.

Summary.—A 38-year-old man with a history of three attacks at short intervals of subarachnoid bleeding (not proved by lumbar puncture), in the third of which he developed unmistakable signs of mesencephalic damage. In this last episode he was completely unconscious for two or three hours, and thereafter stuporose, somnolent and confused in slowly lessening degree for about five weeks. At examination nearly four months after the onset of the third attack he still showed well-marked residual signs of mid-brain type. These included certain Parkinson-like features, and he described changes in his emotional control reminiscent of pseudobulbar palsy. He also complained of defective memory and slowing of his mental processes in general, together with a persistent feeling of not being quite directly in charge of the action of his body. The cause of these latter symptoms is not clear; it would be easy to dismiss them as simply psychoneurotic manifestations, but they give an impression of being organically determined. From his physical signs a mid-brain tegmental lesion must be postulated, predominantly right-sided. Angiomatous malformation seems its most likely pathology, and angiography tends to confirm the diagnosis. In this respect the family history in his sibs suggestive of hæmorrhage from anomalous vessels of eye and brain respectively is significant.

Case 5.—Mrs. Annie P., aged 29, a housewife. No relevant illnesses or family history.

At the age of 18 at a dance suddenly became dizzy and faint. Sat down and held her head low; after a few minutes began to feel better, and lifted her head, only to find that everything was jumping about in front of her eyes. At the same time the left side of her body including her face and tongue became numb and dead. Admitted to local hospital in the early hours of June 6, 1940. She was fully conscious. The pupils were widely dilated, irregular, and fixed. There was nystagmus on lateral gaze, more pronounced looking to right than to left. All forms of cutaneous sensation were much blunted in the left side of the body, the left arm was weak, the left abdominals absent and the plantar extensor. Lumbar puncture gave an evenly blood-stained fluid under slightly increased tension. A week later there was complete paralysis of upward and downward rotation of both eyes, but her other signs had regressed slightly. She was discharged from hospital some six weeks after the onset of illness, with a diagnosis of spontaneous subarachnoid hæmorrhage. She was much better, but there was still palsy of upward and downward gaze, some nystagmus on looking to the right, and slight persisting left-sided hypalgesia. According to the patient the feeling of deadness in the left half of her body lasted without much change for two years or more, after which she gradually became

less conscious of it, though it never entirely disappeared. She married and remained in good health until January 27, 1950, when as she stooped to plug in an electric fire, she felt something click in the back of her head, and was instantly aware that she had gone quite dead down the left side again. She was frightened and lay down on the bed. After a few minutes discovered that she couldn't open her eyes. She remembers her doctor coming to see her, but then lost consciousness and has no recollection at all of the next five weeks. She was admitted to the same local hospital as before, but all that is known of her ten-week stay is that she had bilateral third nerve ophthalmoplegia worse on right than left, left-sided anæsthesia and transient left-sided hemiplegia, and that a diagnosis of spontaneous subarachnoid hæmorrhage was again made. The patient herself says that she was told she was objectively unconscious for thirty-six hours, and after this perpetually sleepy (though she could be roused to recognize and speak briefly to relations at her bedside) throughout the period of weeks for which she is amnesic. She recalls that when she first regained continuous memory, both upper lids were drooping, the right so that she could not see out of it unless she lifted the lid with her hand. With both eyes open she had severe diplopia wherever she looked. The left side was quite numb, but she could move the left limbs normally though she was told they had been useless. When she went home these symptoms were still present in considerable severity but gradually diminished in the course of twelve months.

She was admitted to the Queen Elizabeth Hospital under Dr. Gilbert Hall on May 4, 1951, for investigation. Her chief complaints were recurrent frontal headache, mainly right-sided, and depression over the possibility of further nervous accident. She still had occasional diplopia, but for the most part had learnt to suppress the false image. She had discovered that she could cut her left hand without feeling pain and volunteered that this hand was very slow to recognize when water was too hot to be borne, and that she could bump her left shin without feeling anything but a dull delayed pain. Speaking of sensation in general in the left half of her body, she said "it always takes a moment or two to realize what is happening." She was conscious of a slight left-sided motor disability: in the leg as though something restrained its proper swing after walking a short distance, and in the arm as abnormal hindrance of its use by cold. On examination the following signs were to be made out. Bilateral ptosis, moderately severe on right, slight on left. Divergent squint of right eye, with weakness of internal rotation, loss of upward rotation and some restriction of downward rotation. Movements of left eye full, except downwards. Fine non-persistent nystagmus to right and left specially noticeable in right eye on looking to left. Ocular convergence poor and accompanied by ataxic jerking of eyes with a rotatory component. Pupils equal but eccentric, being displaced nasally and upwards, the right particularly, and irregular. Right fixed to light, left reacting slightly; both contract well on convergence. Left-sided supranuclear facial weakness, evident only in natural expression. Minimal pyramidal signs in left arm and leg, and slight left-sided hypalgesia, depression of tickle sensation and delay in recognition of hot and cold. No objective defect of light touch but subjectively less definite than on right. Appreciation of vibration diminished in left arm and leg. General physical examination negative. X-ray skull and chest normal. C.S.F. pressure and contents normal. C.S.F. and blood W.R. negative. Full blood count and urine examination normal. The patient was thought to be suffering from a vascular malformation of the mid-brain, either angiomatous or telangiectatic. Vertebral angiography was undertaken and the films deemed to show increased vascular shadowing of the upper brain-stem.

Summary.—A woman of 29 with a history of two attacks (at an interval of ten years) of mainly right-sided mid-brain disorder, the first known to have been associated with subarachnoid bleeding and the

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second presumptively so. In the second attack there was apparently loss of consciousness for thirty-six hours followed by pathological drowsiness and resultant amnesia of five weeks' duration. The most likely diagnosis is a brain-stem vascular anomaly.

Case 6.—Barbara B., aged 21, a sewing machinist. This girl first came under the care of Professor W. M. Arnott in June 1947, suffering from auricular fibrillation of rheumatic origin, for which she was treated with digoxin. By this means she was enabled to return to work, and carried on in good health until May 17, 1951, when she suddenly developed pain in the right lower chest and mounting respiratory distress. She was admitted to the Medical Professorial Unit of the Queen Elizabeth Hospital the next day. Examination disclosed signs of pulmonary infarction, in addition to evidence of severe disease of the mitral valve and cardiac enlargement, with irregular action of the heart (rate at apex 120/min., pulse rate 104/min.). She was beginning to recover from the lung embolism when at 5.30 p.m. on May 20 she abruptly became unconscious. Breathing was stertorous and periodic. Pupils widely dilated and fixed. She did not move the right arm or leg or the right side of her face so forcefully as the left on nocuous stimulation. All the tendon-jerks were diminished, and both plantars extensor. Two or three hours later her state was much the same, except the right pupil was now smaller than the left and had become eccentric. She remained quite inaccessible for eighteen hours before her conscious level slowly began to rise. She was pathologically somnolent for a week (until May 28), sleeping almost continuously; she had to be fed and dozed off between mouthfuls, and in medical examination her attention could not be retained more than momentarily. During this period it was witnessed that her speech was slurred, that there was a left-sided ptosis and that she was unable to elevate her eyes. The pupils were still inactive to light, and the right eccentrically placed. She complained of diplopia in all directions. The right lower face and right arm were weak and the plantars extensor. There was no sensory impairment. By June 5 she was quite rational and no longer unduly sleepy, but it was observed that her mental outlook was not yet normal, for she was too easily provoked to laughter and regarded her disabilities unduly lightly.

When seen on June 9 she remembered everything clearly up to the afternoon of her nervous accident, but had no recollection of its exact manner of onset nor any idea of the duration of her amnesia. She was now fully orientated but a little euphoric. She professed herself still lethargic and ready to sleep all day long, and had herself observed that she laughed more easily at little things than she used. She complained that her speech did not come quite naturally, and that she had constant diplopia which prevented her from reading. She said that she could not move her right arm without deliberate effort and that it seemed slow. On examination there was slight dysarthria. No visual field defect. Left ptosis. Downward and inward squint of right eye at rest. Complete loss of upward conjugate gaze. Convergence of eyes very restricted: such movement as there is accompanied by irregular jerking. Pupils equal and circular, but both deviated nasally and upwards, particularly the right, and unresponsive to light or attempted convergence. Right supranuclear facial weakness. Right arm shows a combination of pyramidal and cerebellar motor deficit of mild degree, with similar but less marked signs in the right leg. Both plantar responses still extensor, the right more vigorously, but abdominal reflexes now all present. No sensory disorder but for moderate defect of vibration sense in the right arm and leg. There is little room for doubt that her signs and symptoms were the result of a cerebral embolus, either from the fibrillating left auricle itself or possibly from the infarcted lung, lodging in the upper reaches of the basilar artery. She recovered sufficiently to go home, semi-ambulant, on June 21, 1951.

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Summary.—A 21-year-old sempstress with a history of rheumatic heart disease and auricular fibrillation. She developed a pulmonary infarct in May 1951, and a few days later had brain-stem embolism. She was stuporous for eighteen hours, and in a state of pathological somnolence for a week, with clinical signs of a mesencephalic lesion. In the course of a month she recovered sufficiently to be allowed home, although she still presented well-defined neurological residua.

Discussion

The cases described above have obvious resemblances, and it is clear that the maximum impact of disease fell in each upon the tegmentum of the mid-brain. Since all recovered, no autopsy material is available to prove either the precise limits or the nature of the causative lesions. There are grounds for thinking that the diagnosis in Cases 1, 4 and 5 is an angiomatous or telangiectatic malformation of intrinsic vessels of the brain-stem. Angiography was not successful in Case 3; an alternative possibility here may well be aneurysm of the basilar artery, with spasm and thrombosis of some of its branches to the brain-stem at the time of the subarachnoid leaking. Embolus of the basilar artery appears the explanation of Case 6; the pathological diagnosis in Case 2 is unknown.

It seems a point of interest to ask what may be the exact anatomical locus within the brain-stem, damage to which leads to derangement of consciousness. Until recently it would have been physiologically orthodox to argue, a priori, that the lesion must be so placed as to interrupt the great sensory pathways, an interpretation based upon the views of Bremer (1935). He had shown that the brain of the cat isolated by ponto-mesencephalic section seemed to slumber perpetually, for tracings of its electrical activity revealed large slow waves indistinguishable from those seen in the EEGs of sleeping animals or of animals narcotized with barbiturates. Bremer explained the phenomenon as a deafferentation of the cerebral hemispheres; deprived by stem transection of all somatic and auditory impulses, they could no longer, he thought, be kept alert by the sensory input from eyes and nose alone. By extension, he argued that normal sleep represented a functional deafferentation of similar type, and his theory came to be widely accepted. The correctness of his hypothesis has lately been called in question by the work of Magoun and his colleagues.

In the course of their investigations of the brain-stem reticular formation, it has transpired that this structure is evidently of great importance in sleep and wakefulness. Its localized excitation leads to prompt interruption of the sleep-like EEG rhythm in animals, either under barbiturate drugs or after the fore-brains have been isolated by Bremer's method, and its replacement (whilst the stimulus lasts) by a record resembling the normal wakeful pattern (Moruzzi and Magoun, 1949). It has also been demonstrated (Lindsley *et al.*, 1949) that serial section of the neuraxis, from lower medulla upwards, gradually alters the EEG with an increasing

tendency to synchronization of cerebral electrical activity as the plane of cutting rises, until at mid-brain level a typical sleep rhythm prevails with interminably recurring high voltage slow waves. Further analysis has disclosed that the EEG is not significantly deviated from its normal waking pattern by focal lesions, which destroy the periaqueductal region or interrupt bilaterally the lemniscal and spinothalamic pathways. On the other hand local destruction of the reticular substance in the medial tegmentum of mid-brain and upper pons causes the appearance of a persistent sleep rhythm (Lindsley *et al.*, 1949). Study of animals with chronic injury to this area makes it clear that they suffer a behaviour change, marked by hypersomnolence and diminished spontaneous activity in their waking hours, which is not the case when the reticular formation is spared (Lindsley *et al.*, 1950).

Magoun and his school argue from these results that Bremer's conception is no longer tenable unless the concept of deafferentation be enlarged to include the reticular substance within its scope. They believe the latter plays the cardinal role in the preservation of wakefulness, by offering a constant background excitation directed towards the hemispheres, and in roundabout fashion by virtue of its facilitating effect upon lower motor levels. The great sensory tracts of the brain-stem are, they infer, only important in so far as they provide collateral channels, by means of which the spontaneous activity of the reticular formation may be enhanced.

In the light of this new knowledge from the physiological laboratory, it seems not overbold to suggest that when parasomnic symptoms occur clinically with stem disorders, they indicate encroachment of disease upon the reticular substance. It is a speculation to be proved or disproved by pathological study.

SUMMARY

The histories of 6 patients with brain-stem lesions, affecting chiefly the mesencephalic tegmentum, are described. Amongst other signs, they presented varying degrees of obscuration of consciousness, from exaggerated sleepiness to coma. In view of recent physiological experiment, it is suggested that parasomnia from stem damage indicates disruption of function in the reticular formation.

I must express my indebtedness to Professor P. C. P. Cloake, Dr. G. S. Hall, Professor E. B. C. Hughes and Professor W. M. Arnott for permission to observe and use their cases.

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INTRAVENTRICULAR MEDICATION IN CATATONIC STUPOR

(Preliminary Communication)

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The purpose of this paper is to report some results of the injection of certain synaptic depressant drugs into the cerebral ventricles.

Much evidence has accumulated, particularly in recent years, suggesting that the diencephalic centres exert a regulatory function on cortical activity. Although the connexions between the cerebral cortex and the thalamus have been extensively mapped, hypothalamic and subthalamic pathways are not, as yet, accurately identified (Le Gros Clark *et al.*, 1938; Fulton, 1949; Meyer *et al.*, 1947; McLardy, 1950; Ward and McCulloch, 1947).

Clinical observations, however, together with pathological material and experimental studies have thrown some light on the functions of these regions. The classical studies of Hess (1936, 1946), in which vegetative responses were obtained upon hypothalamic stimulation, found their equivalent in the clinical field in Penfield's observations (1941) on seizures arising in diencephalic structures, and renewed the interest Gowers (1907) had taken more than forty years ago in the borderlands of epilepsy. Bailey's experience with tumours in this area (1933) led him to make experimental lesions in the brain-stem of the cat which produced altered behaviour (1948). Brouwer's (1950) survey of lesions in the hypothalamus and their clinical manifestations provide substantial evidence that vegetative functions, amongst others, are influenced at this level.

The pioneer studies of Dempsey and Morison (1942, 1943) of the electrical potentials of the diencephalon have recently been worked out extensively by Magoun and others, and in their experiments the electrical activity of the cortex was clearly modified both by stimulation of, and lesions in, the thalamus, hypothalamus, and brain-stem reticular formation (Moruzzi and Magoun, 1949; Lindsley, Bowden and Magoun, 1949; Starzl and Magoun, 1951).

Adrian (1947) suggests the presence of central excitatory states with "considerable electrical effects," spreading through the cell masses and cell sheets of the brain. They are probably generated by local dendrite-potentials; the cells of the brain are electrically very unstable and tend to beat either in their own rhythm or respond (quite like the electro-encephalographic amplifiers) to potential changes at a distance, across the insulating myelin and also to very small changes in the biochemical

environment. Thus electric fields are set up, the extent of which in space and time is dependent, or only partially dependent, on the duration and force of afferent impulses. Reverberating circuits may further maintain such fields once they are established.

Recent support for this concept has come from McCulloch (1949).

Such fields of electrical tension might well be taken as the basis of deliria, illusions, and hallucinations of psychotics, or even only of persistent thought patterns in obsessional neurotics; the emotional response to flickering light or beating drums can, as it were, be recorded electroencephalographically. Afferent impulses, whether endogenous or exogenous, are thought to be integrated and arranged in time to amount to an experience at a diencephalic level (Penfield, 1949; Adrian, 1949). That the application of powerful alternating currents to the forehead would alter or interrupt such fields by depolarization of inter-surfaces may be an explanation of the efficiency of electroconvulsive therapy.

Further information through a different approach is available about some of the properties of the diencephalon. Cushing's intraventricular injection experiments (1931) are of considerable relevance. They can be better understood since the publication of Feldberg and Vogt (1948) concerning the transmission of impulses along neuronal chains; they have indicated that in some such chains, at least, transmission is mediated by alternating cholinergic and non-cholinergic synapses. This explains certain apparent inconsistencies in the clinical response to various sympatho- and parasympathomimetic drugs.

In an endeavour to explain the nature of neurosecretory elements common to the pars nervosa of the pituitary and the areas of the tuber cinereum and the hypothalamus, Cushing obtained a paradoxical (i.e. "vagotonic") response to pituitrin by injecting it into the ventricles of patients. This effect was abolished by simultaneous atropine injection. Pilocarpine had an action similar to that of intraventricular pituitrin, whether given systemically, or injected into the ventricles. The characteristic pituitrin response was absent in a patient with a glioma of the tuber.

Cushing found also that acetylcholine injected into the ventricles has an action similar to pituitrin, if less marked. The transience of this action may be due to the quick hydrolysation of acetylcholine by cholinesterase.

Henderson and Wilson (1936) injected acetylcholine into the ventricular system and reported predominantly autonomic effects of this procedure.

The influence of the diencephalon on metabolism is now generally accepted. The order, however, of the association between the higher cortical centres, the diencephalon and metabolism is not clear.

The connexion of mental diseases and metabolic disturbances has come more to the foreground. It should be, therefore, possible to define the part played by the diencephalon in certain mental diseases.

An attempt is made below to suggest relationships between physiological observation and features noted in mental disease.

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Selye's "Alarm Reaction" (1950) is described as "the sum of all biological phenomena elicited by sudden exposure to stimuli to which the organism is, quantitatively or qualitatively, not adapted." It consists of (1) shock, (2) counter-shock, and (3) exhaustion, and this reaction may become a pathological exaggeration in Meduna's oneirophrenia (Meduna, 1950).

The countershock, or alarm reaction proper, leads to Adrenocortical Hypertrophy and a rise of the level of the "Sugar Hormone" (11-dehydroxy –17 hydroxy-corticosterone) output of that organ.

Briefly, the "S-Hormone" raises the blood sugar level and also the amount of stored glycogen by enhancing de-amination of aminoacids and their transformation into carbohydrates. Oxygen consumption, under the ascendancy of the "S-Hormone," is increased—a feature also observed in schizophrenics (Gjessing, *vide infra*) during the period of raised urinary N-excretion. This N-depletion is demonstrated in extreme cases, such as Cushing's disease, by the poverty of skin substance and consequent striation, loss of hair, etc.

The converse state of affairs is guided by the "N-Hormone" (probably testosterone) of the adrenal cortex which favours protein synthesis and nitrogen storage. "S" and "N" hormones, by being catabolic and anabolic hormones respectively, are antagonists; the production of both is stimulated by the adrenocorticotropic hormone of the pituitary; desoxycorticosterone-acetate (D.O.C.A.) governs mineral metabolism; and thus has a direct action on fluid balance.

In the light of Verney's work concerning the antidiuretic hormone (1946), the close interrelation of the posterior pituitary and hypothalamic nuclei assume enhanced significance.

Gjessing (1939) in a long series of most painstaking investigations found that a negative nitrogen balance precedes periods of excitement in schizophrenics by several days. During the period of excitement the nitrogen balance is positive. Oxygen consumption is raised during the former phase and there is a shift towards a lower pH in the acid-base balance. The leucocyte count is elevated.

A rise in the level of the "Sugar" hormone leads to atrophy of thymico-lymphatic tissue; conversely, conditions associated with overgrowth of this tissue show inadequacy in coping with emergencies. This condition may be represented in myasthenia gravis which can then be considered, in a sense, as the antithesis of pathological tension states. A point of particular import is the role played by the acetylcholine-cholinesterase mechanism in the two conditions: Rowntree *et al.* (1950) produced an activation of the psychosis in schizophrenics with di-isopropyl-fluorophosphonate which is an anticholinesterase substance.

Salmon (1932), Nielson (1948), and Major (1949) regard schizophrenia as a diencephalic disease.

From a series of 160 patients who were observed before, during, and after leucotomy, the impression was obtained that the principal change

procured by this operation consisted of an alteration in the speed, size, and maintenance of the patient's reactivity to environmental changes. The bizarre mental states appeared to be secondary to this morbid "emotional" state and once the latter was attenuated by surgery, hallucinations, delusions, compulsions, and other pathological phenomena, in short, many of the apparent disturbances of cortical function in these psychotics tended to regress and disappear. In successful cases the mental improvement was preceded by physical changes of a vegetative nature.

Hypothesis

These observations suggested strongly that the autonomic or vegetative centres are involved profoundly in several forms of mental illness and that in certain forms of mental illness they may, in fact, be the seat of the disease.

Strict division into groups of sympathetic or parasympathetic ascendancy would appear to be inaccurate, because it is unlikely that such a division is possible at high levels of the central nervous system. The division of complex physiological functions into cholinergic and adrenergic phenomena meets with the same difficulties. Within these limitations it is nevertheless considered for the purpose of a working hypothesis that certain mental diseases correspond to a pathological state of autonomic nervous imbalance, probably within the diencephalon. This state may be allied to one of sympathicotonus representing severally the reactions of fight, fright, flight and anger or, to use Meduna's phrase, oneirophrenia.

If this hypothesis is correct, improvement achieved in certain mental diseases, notably schizophrenia, by leucotomy, may be derived from the interruption or suppression of activity amongst the diencephalic centres.

It is proposed here that a more accurate and less mutilating method of treatment might be developed by using drugs locally. The understanding of the natural functions within the diencephalon would also be advanced.

Following these theoretical considerations, it was decided to expose the following drugs to a practical test: cholinesterase in the form of freeze-dried human erythrocyte stroma, procaine hydrochloride, pentamethonium iodide and flaxedil.

Cholinesterase, which as a dry powder had the strength of QACh 250, was made into a suspension with saline; since it could not be sterilized by ordinary methods, it was injected with penicillin (crystalline sodium penicillin G).

The injections into the frontal horn of the lateral ventricle were made by inserting a sharp lumbar puncture needle through the scalp and one of two previously made bifrontal burr holes, or through the old leucotomy trephine opening. In the later injections, a second needle was inserted through the other burr hole to prevent a possible rise in intracranial pressure from the increase in fluid volume, and to permit a

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rapid flushing of the ventricles in case of an untoward response. The dosage of pentamethonium iodide and flaxedil was based upon the presumed average concentration in the body tissues that would result from the minimum clinical dose (20 mg./70 kg. body-weight for pentamethonium iodide and 40 mg./70 kg. for flaxedil) and calculated for 50 grammes of ventricular fluid content. In the case of procaine and cholinesterase, the smallest amount likely to have an effect was taken.

Case 1.—R. G., a woman aged 20, had been ill for five years. For the greater part of that time she had been in deep catatonic stupor, with plastic rigidity; she was bedridden and tube fed. On July 14, 1949, a bilateral pre-frontal leucotomy was performed, followed by a transient improvement during which the patient was ambulant. She returned to her pre-operative state within eight weeks.

The first intraventricular injection was given on April 28, 1950. At this time she was mute, inaccessible, and required every attention including feeding. There was plastic rigidity, the pupils were dilated to 4 mm. diameter, there was marked acrocyanosis with trophic changes in the toes. The dorsalis pedis arteries were not palpable. 22·5 mg. of cholinesterase in 3 c.c. saline with 12,000 units of crystalline penicillin G were injected into the lateral ventricles over a period of ten minutes. The immediate changes in her physical condition were briefly as follows: The blood pressure fell from 150/100 to 105/75; the extremities became warm, the pupils contracted to 2 mm., and the rigidity passed off. After about one hour the patient became co-operative, obeying simple commands, she asked for a bed-pan, took a cup of tea and a biscuit, and generally was now quite accessible. She vomited a little on two occasions. After three hours her extremities became cooler and grey, her pupils started to dilate, her temperature had risen from 97·2 to 101·5° F. and she suddenly became pale and appeared to collapse. Coramine and methedrine were given by intramuscular injection; 10 c.c. of cerebrospinal fluid were withdrawn by lumbar puncture, and replaced by 10 c.c. of saline given intraventricularly. Her general condition improved, although she remained somewhat stuporose for a few hours. She gradually recovered from this state, and was heard humming to herself during the night following the injection. She had a mild febrile reaction for three days. From the day after the injection she fed herself, and was clean in her habits. She became gradually more alert and although she did not speak she responded to commands and took notice of her surroundings. Her peripheral circulation continued to be satisfactory. Two weeks after the injection, she was up and about, dressed herself, read and did needlework, but still did not speak. Three weeks after the injection she started to mutter replies to questions. Seven weeks after the injection she began to earn pocket-money for work done about the wards, she was well behaved, though rather childish, and spent much time in the occupational therapy department doing needlework. At this time her pupils were again dilated, her blood pressure and pulse-rate had returned to 135/80 and 105 respectively. The reflex tone in her muscles had risen once more.

On June 16, 1950, 5 mg. of cholinesterase in 1 c.c. saline and with 10,000 U. penicillin were injected. Eight minutes after the injection her face became flushed and at fifteen minutes she had a major generalized convulsion, with focal onset in the left arm. Phenobarbitone was administered by intramuscular injection immediately, but she had a further three fits within the next two hours. A hæmatoma had appeared at the puncture site; a lumbar puncture was made and 20 c.c. of pale pink cerebrospinal fluid were withdrawn. After this she fell asleep. It was felt that the fits had been due to a local cerebral hæmatoma from the needle puncture. For the next few days she was incontinent of urine, but by seven days after the second intraventricular injection she had complete control over her bladder. At this time she talked freely, ate ravenously; there had been no more fits. Seven days later she was able to attend the hospital dance. About four weeks after the

injection she exhibited some odd postures and was worried by other patients. She complained of being "nervy." Nevertheless two weeks after this she went for the annual hospital outing to the seaside; she made considerable preparations for this occasion, obtaining a new "hairdo" and taking great care in dressing. She enjoyed the outing greatly.

The following morning she was found in bed in catatonic stupor, and for the following three weeks she spoke very rarely, was incontinent, and had to be tube-fed; there was no grey cyanosis as before.

Two subsequent intraventricular injections of cholinesterase: 2 mg. on August 25, and 15 mg. on August 29, 1950, had very little effect. The same material was given to another patient without effect, and it was therefore concluded that the preparation had deteriorated. As no more supplies could be obtained, no further injections with this drug have been possible.

On October 27, 1950, 1 mg. of procaine in 5 c.c. saline was injected intraventricularly. This had only a slight effect at the time, but there was a further improvement in her state over the subsequent three weeks.

By December 17, 1950, she was eating voraciously and had gained considerably in weight. Although ambulatory, she lapsed at times into mild stupor, but there were frequent intervals of activity, albeit, at times mischievous activity; never, however, did she become hostile or resistive. Her pupils continued to be large, but otherwise there were no outstanding signs of autonomic dysfunction. In an attempt to obtain further improvement, after a preliminary removal of 10 c.c. of C.S.F. she was given 0·015 mg. of pentamethonium iodide in 10 c.c. of saline, intraventricularly, and slowly, over a period of twenty-five minutes. There was a fairly marked change, as in the case of the first injection of cholinesterase, the first signs appearing within about thirty seconds. The following three weeks she was lively and euphoric, at times incongruously merry and laughing; her speech was pert. She went to the hospital Christmas dance. About ten days after the dance she was able to recall it, and went into fits of laughter at the memory of it.

On January 5, 1951, a second intraventricular injection of pentamethonium iodide was made. This injection was made fairly rapidly. Her pupils contracted to about half their previous size within five minutes, and her blood pressure unexpectedly rose this time from 148/95 to 160/95. Within about thirty minutes she demanded a pot and was annoyed and talkative about it. Her blood pressure returned to 140/90; it is possible that the transient rise was caused by some pain at the needle puncture. She was quite alert at the time.

On January 12, 1951, 0·015 mg. pentamethonium iodide were again injected with a similar immediate and delayed effect as before.

On January 19, 1951, 0·03 mg. of flaxedil in 10 c.c. saline were injected intraventricularly. The effects were similar to those occurring after pentamethonium iodide, but were less marked. They did not last more than a day or two, and by January 26 she was again inaccessible, and showed no free speech.

On January 26, 1951, a final injection of pentamethonium iodide was administered. Double the previous dose, that is 0·03 mg., were given. The blood pressure rose quickly from 115/80 to 130/75; her pulse-rate did not change but she became flushed, perspired and salivated profusely. She muttered comments and became fairly alert. Ten days after the injection she was still bright and taking an interest in all that went on. She was well behaved, except for occasional mischievousness, and passed much of her time reading. On the whole, she was considerably improved from her erstwhile stupor, but she was not as well as she had been after the first two injections of cholinesterase.

Case 2.—D. R., a man aged 38, had been ill for six years. At the onset of the illness he was depressed and quiet, but soon he became inaccessible, at first with some restlessness, later growing quiet. He showed very little spontaneous movement, no speech, and required every attention including feeding. He had two courses of electroshock therapy early in his illness with only transient effect. At

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the time of this investigation the only activity displayed was negativistic resistance; he was then stuporose with the characteristic grey cyanosis and trophic skin changes.

On September 29, 1950, 5 mg. of cholinesterase in 0·5 c.c. of saline and with 5,000 U. penicillin were injected through a frontal burr hole into the left lateral ventricle. There was no clear effect from this injection.

On October 27, 1950, 3 mg. of procaine in 3 c.c. of saline were injected intraventricularly. The only unequivocal effect from this was a profuse vomit of about 2 pints of clear watery gastric juice.

On December 17, 1950, 0·03 mg. of flaxedil in 10 c.c. saline were injected slowly, the whole injection taking twenty minutes. By the end of the injection the pupils were reduced from 4 mm. to 2 mm. diameter, and there was a dramatic change in the state of his skin, which became warm, pink and of normal appearance. At the onset of the injection the patient was rigid and inaccessible; within ten minutes after the end of the injection he was relaxed and co-operative to the extent of obeying simple commands. Thirty minutes later he was looking round and watching proceedings with evident interest. He did not speak, and returned to his previous state within twenty-four hours.

On January 5, 1951, 0·015 mg. of pentamethonium iodide in 10 c.c. saline were injected intraventricularly; the effect of this injection was more marked than the previous one. Within twenty minutes the patient talked and spontaneously asked for food which he consumed with great appetite. Two days later he was able to converse with his father when visited. After three days he relapsed into his previous state.

Three further intraventricular injections were given: on January 12, 0·015 mg. pentamethonium iodide, on January 19, 0·03 mg. flaxedil, and on January 26, 0·03 mg. pentamethonium iodide. After this he remained better, being less resistive, of healthier colour, and eating spontaneously. This was his state when last observed on February 9, 1951.

Case 3.—E. B., a woman aged 36, had been ill for eight years. Early in her illness she had had manic phases but later passed into a state of catatonic stupor, and had remained in this state for several years. She showed less marked skin phenomena than the other two cases. Her pupils were persistently dilated, never being smaller than 3 mm. diameter. She had two intraventricular injections of 0·015 mg. pentamethonium iodide in saline on January 5 and 12, 1951, and 2 injections of 0·03 mg. flaxedil on January 19 and 26, 1951, respectively. The effects of the injections were least marked in this case. She was in a state of catatonic supor before the injections, and afterwards would open her eyes, and exhibit a mild interest in her surroundings. She acquired a blink reflex to threatening gestures which had not been there before, and she could now be induced to hold out her hand and follow an object with her eyes, neither of these being possible to elicit before the injections. She was in this state up to February 9, 1951, when she was last examined.

Summary

Some of the available evidence for the nature of the disorder underlying catatonic stupor is discussed and arguments are presented for the clinical trials carried out.

The clinical effects of injections of each of four drugs into the lateral cerebral ventricles in cases of schizophrenia are described. The drugs used were: (1) Cholinesterase, (2) Procaine, (3) Pentamethonium iodide and (4) Flaxedil.

Three cases were treated. In the first case all four drugs were used; in the second case cholinesterase, pentamethonium iodide and flaxedil, and in the third case pentamethonium iodide and flaxedil. The effect

aimed at was to relieve the condition of catatonic stupor. This effect was achieved to a varying extent in all three cases, and was most marked with cholinesterase in Case 1, and pentamethonium iodide in the three cases.

My thanks are due to Dr. A. G. Duncan, Medical Superintendent at Severalls Hospital, Colchester, for the opportunity to do this investigation and for permission to publish this report. To Dr. R. H. F. Smith I am particularly indebted for his help in general and in selecting and supervising the patients, and for his interest. It is a pleasure to express my gratitude to Miss D. J. K. Beck of the Middlesex Hospital for her invaluable encouragement and kindness, and to Dr. Warren S. McCulloch for his active interest in this paper and for the opportunity to pursue the problem farther.

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THE NEUROLOGICAL MANIFESTATIONS OF IDIOPATHIC HYPOPARATHYROIDISM

BY

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THAT deficiency of parathyroid hormone secretion results in hyperexcitability of the peripheral nervous system (tetany or spasmophilia) is well known, but the other neurological manifestations of the tetany syndrome are less familiar and have been little discussed in the British literature. Two cases of idiopathic hypoparathyroidism are here presented with special regard to the neurological problems. Other features of these cases will be reviewed elsewhere.

Case 1.—A. H., male, aged 9 years. The child, one of two sibs, came from a family with no history of fits or other nervous disease. He had a normal full-time birth and was bottle-fed until weaned at 1 year. He is stated to have walked at 1 year but did not learn to speak until the age of 4 or 5 years.

He had measles at age 3 and chickenpox at 5. He has had two or possibly three attacks of pneumonia. During the first of these in 1944 he had a convulsion but he was otherwise free from fits until 1947 when, at the age of 5, he took chickenpox.

Shortly thereafter he began to have seizures. These occurred in spells during which he had several attacks per day, and then there were long intermissions. The attacks were not completely controlled by phenobarbitone, 2 grains daily, prescribed at a Children's Dispensary. After six months' intermission, daily seizures started in December 1948. During the next month he became nauseated and vomited, with the development of an upper respiratory infection, so his mother stopped his phenobarbitone.

He was admitted to the Southern General Hospital, Glasgow, on 25.1.49 and was then complaining of headache every morning. The upper respiratory infection was treated with penicillin inhalations and general tonic measures which included cod-liver oil and "Adexolin." Fits were controlled with phenobarbitone. It was noted that the fits ceased when inhalations were discontinued. Clinical examination revealed no evidence of abnormality of the nervous system apart from a convergent strabismus which he had had since infancy. The fundi are stated by two observers to have been normal at that time. Several fits were recorded by other observers who describe twitching of the right arm and leg with deviation of the eyes to the right. This conformed to the mother's description of a previous fit. One observer noted that as one attack passed off there was tonic spasm of the right leg with flexion and inversion of the foot. The significance was not appreciated and the case was discharged with a diagnosis of idiopathic epilepsy, X-ray of skull and chest being considered normal.

The child was re-examined at the Follow-up Clinic at intervals of one to three months and there was no occasion to reconsider the diagnosis as he remained free from fits except when his dose of phenobarbitone was reduced in May 1949. He was then at a special school, since he was unable to read or count. He was considered to be mentally defective while in hospital, though his mother attributed his defect

to his poor eyesight. In June attention was drawn to his nails which were brittle and cracked longitudinally, with transverse white streaks. Calcium lactate was prescribed.

Diphtheria prevented the child from attending until January 1950. He had been relatively free from fits but was complaining of more marked headache and blurring of vision. Ophthalmoscopy (and later slit-lamp examination) revealed punctate opacities scattered throughout both lenses, most marked in the posterior subcapsular zone. A provisional diagnosis of chronic hypoparathyroid tetany was then made and the patient was readmitted for further investigation on 11.2.50.

Examination revealed marked delay in dentition. The incisor teeth were notched and the enamel transversely ridged. His skin was rather dry but within normal limits. Hair distribution and formation were normal. Skeletal development was delayed by about two years, but of normal proportion. He was very fidgety and grimaced constantly, but this choreiform state subsided in about a week. Chvostek's sign was markedly positive and Trousseau's slightly positive (requiring twenty to thirty minutes). Neurological examination was otherwise normal. No abnormality of other systems was detected; the pulse was regular and the blood pressure 90/65 mm.Hg.

When fits were observed in the ward, some were typical carpopedal spasms of tetany while others were indistinguishable from right-sided or generalized major epilepsy (with loss of consciousness). On 21.2.50 he had an attack resembling delirium tremens in which he became very frightened because of "something in his bed" from which he had to escape. He settled with sedation, but for two weeks his behaviour was unusual. He knocked his head against the bars of the cot, tore the bedclothes, jumped about the cot and attempted to climb out. Any restraint was fought bitterly. Even when this state subsided he remained difficult to control and was the "problem child" of the ward; he bit the nurses and fought with other children, though his mother described him as a normally good-natured child.

He continued to have fits while metabolic studies were carried out, but these stopped when treatment was started and did not recur, even during an attack of mumps in April 1950, until his mother stopped treatment in October 1950, as a urinary test for calcium showed hypercalcuria (fig. 2).

TABLE I.—BIOCHEMICAL DATA

	Case 1 (A. H.)	*Case* 2 (H. T.)
Total serum calcium ..	5·0–7·2 mg. per cent	7·0 mg. per cent
Serum inorg. phosphorus..	6·4 mg. per cent	4·5 mg. per cent
Serum alkaline phosphatase	5·5–10 K.A. units	5·6–8·2 K.A. units
Serum potassium	18–20 mg. per cent	19 mg. per cent
Total plasma proteins ..	8·15 grammes per cent	8·31 grammes per cent
Blood urea	37–44 mg. per cent	31 mg. per cent
Urea clearance (Van Slyke)	93 per cent	62 per cent
Alkali reserve	68·5 vols CO_2 per cent	61 vols CO_2 per cent
Calcium balance ..	+75·3 per cent–+34·5 per cent	—
Phosphorus balance	+86·4 per cent–+68·3 per cent	—
Fat balance ..	+91·9 per cent–+96·5 per cent	—

The biochemical findings establishing the diagnosis are listed in Table I. Renal function, fat absorption, and the alkali reserve were normal. Radiology of the skeleton showed unusual degree of calcification. The ribs and pelvis were generally denser than normal. The spine showed coarse vertical trabeculation and horizontal growth lines. There was unusual sclerosis on each side of the diploic channel running through the bodies of the fourth to tenth dorsal vertebræ. The long bones

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showed many marked growth lines but were otherwise within normal limits. There was about a year's delay in the wrist ossification. The skull sutures were slightly wider than normal for the age and there was calcification of the choroid plexus. The position of the intracranial calcification was confirmed by stereoscopy (Dr. D. C. Suttie). The roots of some of the teeth were shortened, especially the incisors.

Electroencephalograms (E.E.G.) were recorded before treatment (March 2, 1950) and when the serum calcium was approaching normal (June 5, 1950) (fig. 1). The initial record shows a gross generalized dysrhythmia characterized by high-voltage delta activity. The predominant frequency is 3–4 c/sec. The later record shows a general speeding up (predominant frequency 8–9 c/sec.) with a marked shift in

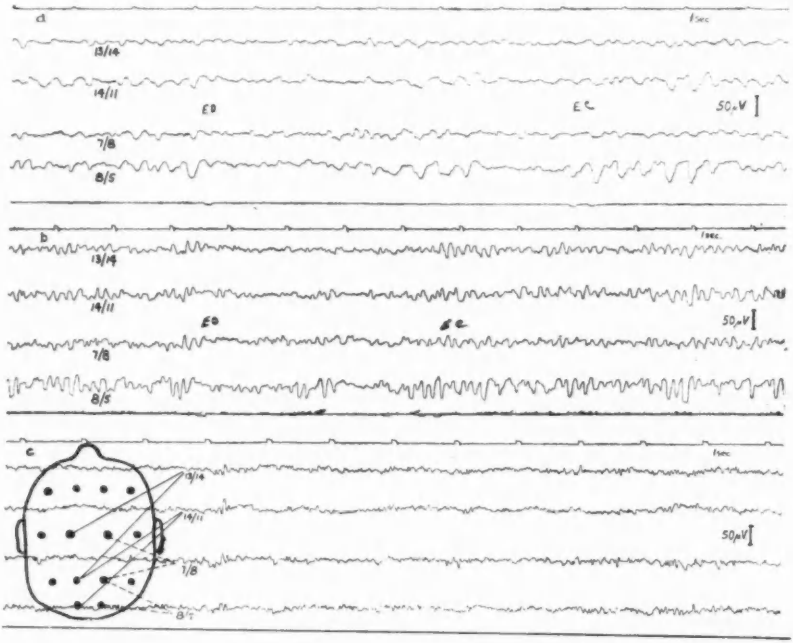

FIG. 1.—(*a*) *Case A. H.* 2.3.50 (*serum calcium* 5·0 *mg. per cent.*) 3–4 c/sec. and 6 c/sec. waves predominate in all leads bilaterally. The patient could not be induced to hyperventilate. (*b*) *Case A. H.* 5.6.50 (*serum calcium* 9·8 *mg. per cent.*) The predominating frequency is 8–9 c/sec. but there are frequent delta complexes (2–4 c/sec.) especially in the parieto-occipital leads bilaterally. Hyperventilation increases delta activity and raises the voltage. (*c*) *Case H. T.* 18.1.51 (*serum calcium* 7·7 *mg. per cent*). The record shows a mild non-specific dysrhythmia with a predominating 9 c/sec. and 15 c/sec. frequency with occasional 5–7 c/sec. waves. Hyperventilation increases the voltage but the wave-pattern is unchanged. (High frequency muscle potentials have been filtered out of the record.) E.O.—Eyes open. E.C.—Eyes closed.

the basic rhythm toward the alpha frequencies, but delta complexes are still present in all areas. During a relapse in October 1950 with frequent attacks of tetany and serum calcium 6·8 mg. per cent, Erb's test gave a C.O.C. at 7 milliamps.

A psychometric examination carried out by the Glasgow Education Health Service (reported by Dr. E. A. Allan) in April 1951 revealed that the patient, at a chronological age of 10 years, had a mental age of 4 years. Reading and arithmetic standards were those of a child aged 4 years and 5 years respectively. The I.Q. was 48. His teacher did not consider that his poor visual acuity was a maior contributory cause to his very slow progress at school.

Case 2.—Mrs. H. T., aged 46. The patient was admitted to Dr. D. K. Adams' wards in the Western Infirmary, Glasgow, in March 1949, for investigation of fits. She had first complained of a "nervous breakdown" after her father's death when she was aged 28. For sixteen months her only complaint was unusual tiredness, then she began to have severe generalized headaches which lasted for three months. As headache passed off, attacks of stiffness of both hands occurred during the subsequent six months, usually in the morning. She remained well for the next fourteen years, except for one fainting attack for no apparent reason in 1946, but a routine eye examination in that year revealed early cataract which matured very rapidly so that the right lens was removed in September 1946, and the left in January 1947. In May 1947 an operation on the left eye for prolapse of the iris was followed by excessive fatigue. Subsequently she complained of mid-sternal dysphagia; otherwise she remained reasonably well until early January 1948, when she began to have frequent headaches and to drag her right foot periodically, during spells of sudden onset and of a few seconds duration. During the next three to four months the whole of the right leg became involved in these attacks, and subsequently the right upper limb also, the latter assuming the "main d'accoucheur" position. In a further three to four months the left arm and leg became involved. No clonic spasms or muscle twitching occurred and consciousness was never lost. During an attack she was unable to speak but was fully aware of her environment. There was no tongue-biting or incontinence, and no automatism or abnormality of affect succeeded the fits. Initially spasms were of momentary duration but gradually became longer until they lasted for ninety minutes, before admission to hospital. For eighteen months before admission she complained of headache.

She had had a completely healthy childhood, free from zymotic diseases. Her finger nails were brittle and split along the edges. Though now edentulous she believed her dentition had been normal. During severe tetany her scalp hair was shed, but grew in again when tetany was controlled.

The fits observed in the ward were typical carpopedal spasms without loss of consciousness. Chvostek's and Trousseau's signs were present. No neurological abnormality was detected except slight nystagmus to the left and absent abdominal reflexes. The blood pressure was 120/80 mm.Hg.

Radiology showed no abnormality of the skull and no intracranial calcification. There was partial collapse with wedging of the sixth dorsal vertebra and the dorsal vertebræ generally showed osteoporosis. The phalanges of the hand showed a mixture of sclerosis and osteoporosis with sclerosis predominating. There was osteoarthritis of the hip and sacro-iliac joints, and ossification of the left iliosacral ligament. No other soft-tissue calcification was seen.

An E.E.G. on 18.1.51 showed a mild non-specific dysrhythmia with predominating frequencies of 9 c/sec. and 15 c/sec. and isolated 5–7 c/sec. waves (fig. 1).

Symptoms were rapidly relieved by restoration of the blood calcium and phosphorus levels with calciferol and calcium gluconate in the amounts shown in fig. 3. Treatment was controlled by regular blood examination. In January 1951 the serum calcium had dropped to 7·7 mg. per cent and on questioning she admitted to excessive fatigue, muscular weakness, and stiffness of the hands at her menstrual periods.

The biochemical changes are summarized in Table I and will be considered in more detail with the non-neurological features elsewhere.

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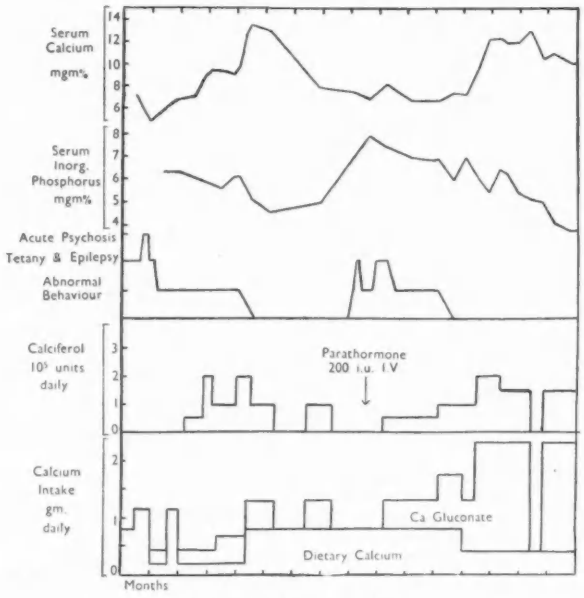

FIG. 2.—Case A. H.

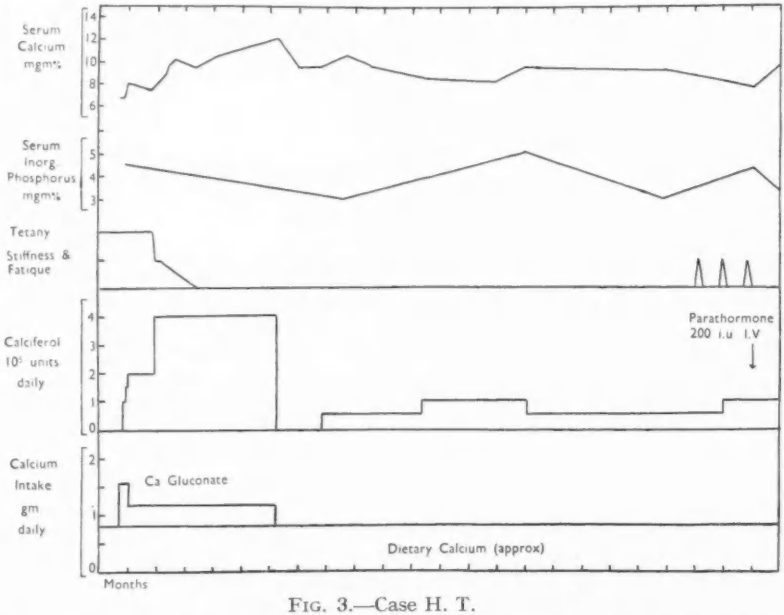

FIG. 3.—Case H. T.

FIGS. 2 and 3.—The changes in serum calcium and inorganic phosphorus and their correlation with symptoms. Calcium lactate and calcium gluconate were used in treatment. The charted level of calcium intake is shown as elemental calcium (13 per cent of calcium lactate; 9 per cent of calcium gluconate). Except for the balance periods in fig. 3 the dietary intake of calcium is an estimated approximation.

Cerebral Disturbances in Hypoparathyroidism

The most common abnormality of the nervous system in parathyroid deficiency, whether spontaneous or post-operative, is tetany which results mainly from hyperexcitability of the peripheral nervous system as described later. There is experimental evidence, however, that the central nervous system is also involved (Noël Paton, Findlay and Watson, 1916).

Albright and Reifenstein (1948) describe the signs of tetany, in order of appearance, as:—numbness of the extremities (the most constant), cramps of the extremities, carpopedal spasms, laryngeal stridor, and generalized convulsions. It is not generally realized that typical epileptiform convulsions occur as a manifestation of tetany even in the absence of the classical carpopedal spasms. This was a feature of Case 1 when first seen, though pedal spasm was noted after one fit. The literature does not emphasize that the epileptic or tetanic seizure may be unilateral (Shelling, 1935). Kugelberg (1948*b*) states that hemitetany is rare and is usually seen in cases with extensive cerebral lesions. Wilson (1944) cites five reports confirming this opinion but mentions a case in which hemitetany preceded more severe bilateral tetany and refers to a similar case of Gowers'. In the present cases the same sequence was seen. Redlich (1911) collected 72 cases of tetany associated with epilepsy, including 11 of his own. At least 21 of these were associated with post-strumectomy tetany. Further series are reported by Kräpelin (1890), Hoësch (1937*a*), Sutphin, Albright and McCune (1943), Taubenhaus and Engle (1945) and Gotta and Odoriz (1948). Single cases of epilepsy appearing for the first time after parathyroidectomy were reported by Lisser and Shepardson (1929), Shelling and Goodman (1934) and Kowallis (1941).

Headache, which was severe in both cases, has been noted previously (Lachmann, 1941; Blum, 1941; Levy, 1947). Hoësch (1937*b*) described cases of hypoparathyroidism in which "migraine" was the only symptom and attributed it to vascular spasm. Vascular phenomena occur elsewhere in tetany, being described as a cause of abdominal pain. Quincke's œdema has been noted (Lachmann, 1941).

The association of epilepsy, headache, progressive loss of vision and separation of cranial sutures in Case 1 created a symptom complex suggestive of an intracranial space-occupying lesion. The state of the eyegrounds could not be determined after cataract developed. Increased intracranial pressure with bilateral choked discs was observed in idiopathic hypoparathyroidism by Albrecht (1924), Shelling and Goodman (1934), Barr, MacBryde and Sanders (1938), Sutphin, Albright and McCune (1943), Leonard (1946) and Levy (1947).

Signs of disease of the basal ganglia have been reported (Gsell, 1950) and the present Case 1 had a choreiform episode. Symmetrical bilateral punctate calcification of the basal ganglia is relatively common. Originally described by Fritzsche (1935) its relationship to hypopara-

thyroidism was noted at the Mayo Clinic (Eaton and Haines, 1939; Siglin, Eaton, Camp and Haines, 1947). Camp (1947) reviews the 12 cases seen at that Clinic and discusses the differential diagnosis of calcification of the basal ganglia. In 5 of the 12 cases there was also radiological evidence of calcification in the deeper layers of the cerebral cortex and in the cerebellum. Calcification of the white and grey matter of the cerebral hemispheres as well as in the basal ganglia was confirmed at autopsy by Engfeldt and Gentele (1950). The cerebral calcification, in common with other soft-tissue calcification in hypoparathyroidism, occurs perivascularly. Symmetrical intracranial calcification was seen in Case 1 but stereoscopic investigation (Dr. D. C. Suttie) showed that it was situated in the choroid plexus and not in the basal ganglia. No intracranial calcification was detected in Case 2. The radiological appearances are further discussed by Lowenthal (1948) and Chavany, Bogaert and Houdart (1949).

Peripheral Nervous System in Tetany

As is well known, tetany occurs in many diseases but, whatever its ætiology, it is accompanied by an increased excitability of the peripheral nervous system. This may be so marked that muscle groups go into tonic spasm producing the well-known "main d'accoucheur," a similar pedal spasm, and laryngismus stridulus if the laryngeal musculature is involved. Twitching and fibrillation of the muscles are rare in man but are common in experimental tetany produced by removing the parathyroid glands of dogs (Noël Paton and Findlay, 1916).

Tetany may remain at a subclinical level, being then termed "latent tetany." Case 2 and others in the literature (Boothby, 1932; Ketcham, 1936; MacBryde, 1938; Margolis and Krause, 1939; Cantor and Scott, 1942; and Levy, 1947) suggest that excessive muscle weakness and fatigue may precede tetanic spasm. The presence of latent tetany is determined by demonstration of increased neuromuscular excitability. Of the numerous methods (Selye, 1947) three have been accepted by tradition as suitable for routine clinical use, and are termed Chvostek's Sign (1876), the Trousseau Phenomenon (1868), and Erb's Test (1874).

The Chvostek sign (contraction of the facial muscles of expression unilaterally on percussing the facial nerve in front of the ear) is indicative of hyperirritability of the facial nerve, with certain reservations. Shelling (1935) considers it to be a fairly reliable method for demonstrating latent tetany. He believes it to be most trustworthy in the tetany of infants, for, up to the second year of life, it is rarely found in any other condition, except in some cases of meningitis and occasionally in normal infants during their first week of life. "After the second year," he states, "the sign occurs not infrequently in apparently normal individuals and after the fifth year it should not be relied upon unless corroborated by other diagnostic aids." Albright and Reifenstein (1948) confirm this statement but add that contraction of the muscles of the

eyelids as part of the Chvostek response is rarely present except in untreated hypoparathyroidism. The Chvostek sign was absent in 73 per cent of 32 cases of latent tetany investigated by O'Donovan (1948). Graham and Anderson (1924) found Chvostek's sign to be positive in 29 per cent of 1,723 juveniles with no clinical or biochemical evidence of hypocalcæmia. Römer (1923) has noted it in 16 per cent of epileptics.

Shelling (1935), Lachmann (1941) and Albright and Reifenstein (1948) remark on the frequent absence of the Trousseau phenomenon (carpal spasm induced by tourniquet ischæmia of the upper arm) in marked cases of hypoparathyroidism. O'Donovan (1948) found it negative in 34 per cent of observations in latent tetany. Shelling (1935) states that it is not to be regarded as pathognomonic of latent tetany. Kirstein and Kugelberg (1946) found it present in 4 per cent of normal subjects. The Trousseau phenomenon has recently been investigated electromyographically by Kugelberg (1946, 1948*a* and *b*). He draws attention to the fact that pressure ischæmia of the nerves in the proximal part of the arm causes all the carpal symptoms of irritation seen in spontaneous tetany in identically the same way with regard to sequence and distribution. Tactile paræsthesiæ, fasciculation, the sensation of spasm, and the spasm itself appear in that order, beginning peripherally and spreading centripetally. Spontaneous activity was found to originate in the ischæmic peripheral nerve fibres, appearing first in the longest fibres and affecting various types of fibres in an order which was identical to that of their sensitivity to stimulation by a slowly rising current of electricity. The distribution and order of activation of different tactile and motor fibres in the arm in ischæmia was also found to correspond well with the order of paralysis in more severe ischæmia. He remarks (1948*a*) that the same sequence of irritation and paralysis is noted where the cause is a transient cerebral circulatory disturbance, as in migraine. Local circulatory differences may be the explanation for the occurrence of hemitetany with extensive central nervous system lesions (1948*b*).

The threshold for ischæmic irritability (1948*a*) or for iterative (double-spike) response to slowly rising or constant electric current was found to be lowered by hyperventilation or by hypocalcæmia (1948*b*) and all three factors may combine. This forms a satisfactory explanation for the phenomenon, noted by von Bonsdorff (1930), of production of tetanic spasm by hyperventilation after preceding compression of an arm (O'Donovan, 1948). Flick and Hansen (1925) suggested that the Trousseau phenomenon was reflex in nature as, in dogs, they claimed to abolish it by nerve block proximal to the cuff. The earlier excitation of afferent fibres might have supported this theory but Kugelberg (1948*a*) found that proximal novocain block did not abolish the phenomenon in man.

In Case 1 the Trousseau phenomenon could only be elicited if the sphygmomanometer cuff (inflated above systolic B.P.) was kept in position for about twenty minutes and eventually could not be elicited

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though the serum calcium was low and Chvostek's sign markedly positive. This finding is of interest in view of the antagonism, exhibited by Paton, Findlay and Watson (1916), between peripheral nerve excitability and that of the central nervous system in parathyroidectomized dogs and cats. In childhood, the electrical excitability bears a closer relationship to the severity of symptoms, e.g. carpopedal spasms, laryngismus stridulus, and the facial phenomenon. They consider the facial phenomenon to be even more delicate than the increased electrical excitability as an indication of latent tetany as it often persists for a considerable time after the electrical excitability has reached a normal level. This was also noticed by Harvier (1909) and was confirmed in Case 1.

In Erb's Test, the electrical excitability of the peripheral motor nerves is estimated by measuring the twitch-threshold for galvanic stimulation. The C.O.C. is usually preferred to the A.O.C. as, though less delicate, it is easier to interpret. A C.O.C. elicited with less than 5 milliamps is usually diagnostic of tetany. Infants under 1 year are usually less responsive than older children, the adult threshold being reached about the fifth year (Shelling, 1935). During a period of frequent attacks of tetany, Case 1 had a C.O.C. of 7 milliamps. Bourguignon (1923) and others consider the chronaxie to be a better indication of nerve excitability. Recent opinion (Kugelberg, 1948*a*) is that the most sensitive index of nerve excitability is its "time-constant of accommodation" (Hill, 1936). The accommodation of the nerve to the passage of an exponentially rising current is measured. Reduction in ionized calcium in the blood results in increase in the "time-constant of accommodation," that is the neuromuscular tissues accommodate less readily and are thus excited by relatively slow rates of change in the strength of the stimulating current. If the calcium-ion concentration is sufficiently low there may be a complete absence of the phenomenon of accommodation.

Hyperirritability of sensory nerves can also be demonstrated (Hoffmann, 1888).

Psychological Changes in Hypoparathyroidism

Mental retardation, as shown by Case 1, has been observed previously, though Albright and Reifenstein (1948) state that this usually occurs in long untreated cases. Mortell (1946) has recently reported a case with impaired intellectual function assessed by standardized psychological tests. There was no improvement of intellectual function despite satisfactory clinical response to treatment. Previously progressive personality changes were thought to have improved as in Case 1 of the present report. Shelling (1935) states that "tetany is seldom, if ever, accompanied by loss of consciousness or by permanent changes in mentality. Hallucinations or mild confusions may occur during and after attacks of tetany, or even during apparently tetany-free periods.

In some patients, a change in mood may be noted, in others temporary mental dulness and enfeeblement may be an outstanding feature. These mental changes are more common in the tetany following strumectomy than in any other form, and they are probably due in part to the associated hypothyroidism from which these patients usually suffer."

The literature was reviewed in 1920 by Barrett who found no evidence of a specific psychosis in tetany and attributed the mental changes found among tetanic patients to various causes, and only indirectly to their tetany or convulsions. Psychosis after parathyroidectomy was reported by Beck (1928), Snapper (1930), Mandl (1933), and Knospe (1938). Interest was reawakened by the paper of Greene and Swanson (1941) who reported 18 patients with hypoparathyroidism, of whom 5 (all post-operative) had an associated psychosis. They agreed that no type of psychosis could be regarded as characteristic of hypoparathyroidism but the usual type was toxic delirium. In their opinion such a psychosis, if it develops, occurs within three or four months of the onset of the tetany and might persist for several months, recovering without residual damage to the central nervous system when the blood calcium level is maintained at normal. Hoskins (1942), in an editorial comment on Greene and Swanson's paper, quotes "the older literature" (no references). He states that Timme had noticed marked irascibility which responded to calcium and sunlight, and that Shannon had reported improvement in 6 cases out of 8 treated with parathyroid extract. His cases were children with convulsions followed by depression and irrational speech. As the condition progressed they had night terrors and acute maniacal excitement with screaming, fighting, and tearing of their clothes. This description is strikingly similar to the acute psychosis of Case 1, in which there were also hallucinations and a resemblance to alcoholic delirium tremens.

In addition to the more common toxic delirium, Greene and Swanson found other types of psychosis, including dementia. In 2 of their cases the hallucinations were of a sexual type and in both instances the eroticism had been markedly augmented prior to the onset of the psychosis. In 2 other cases delusions of persecution with attempted suicide occurred. Less severe nervous symptoms described by Greene and Swanson were anxiety, depression, and a sense of impending disaster. Emerson, Walsh and Howard (1941) describe a case with an acute depressive psychosis. The psychiatric aspects of this case are further discussed by Richter, Honeyman and Hunter (1940) who describe cyclical alterations in her mental status. Acute confusional psychosis of several weeks' duration occurred in the idiopathic case of Cantor and Scott (1942). A single case occurring thirteen years after thyroidectomy had seizures, delusions, hallucinations and manic-depressive episodes (Scarlett and Houghtling, 1944). Blum (1941) gives a long list of vague symptoms, often classified as functional nervous disorders, which he believes to be caused by latent chronic hypoparathyroidism. On the

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other hand psychosis has been reported in hyperparathyroidism. The literature is reviewed by Eitinger (1942).

Electroencephalographic Changes

Gotta and Odoriz (1948) describe the E.E.G. in hypoparathyroidism with tetany and epilepsy, 3 of their 14 cases being spontaneous. The E.E.G. shows a predominant alpha rhythm (10 c/s) or a fast (20 c/s) rhythm with slow waves (2–5 c/s) singly or in series, with occasional spiking. Spikes and slow waves rarely occur together in the same case. The slow waves are sometimes generalized, but usually localized especially to the frontal region. When generalized they appear in the frontal region and spread to the parieto-occipital. The changes are enhanced by hyperventilation but are not affected by the intravenous injection of calcium. There is a tendency to restoration to normal if the blood calcium level is raised by calciferol, the basic rhythm (alpha or fast) remaining, but with fewer slow waves. Hyperventilation then causes less pronounced changes. In their opinion the patterns are not specific and can occur in epilepsy from other causes. A normal record may be found. The E.E.G. of tetany is further discussed by Odoriz, del Castillo, Manfredi, and de la Balze (1944), and Mortell (1946). Sutphin, Albright and McCune (1943) describe a record obtained during attacks in their patient (who had papillœdema) as "grossly abnormal but without evidence of localization." Single cases are described by Kowallis (1941) and Taubenhaus and Engle (1945). In the first case presented above (fig. 1), the pre-treatment record showed diffuse slow activity (3–6 c/s) with increased voltage during hyperventilation. A later record taken when the serum calcium level was about normal, showed speeding up of the cortical rhythms (8–9 c/s) but bursts of delta activity still appeared in all areas, especially after hyperventilation. The second case had a mild non-specific dysrhythmia with mainly 9 c/s and 15 c/s activity but occasional 5–7 c/s waves. We do not consider this record to be definitely abnormal.

Discussion

The ætiology, pathogenesis and non-neurological features are to be discussed elsewhere (Simpson, —). Sabbatini (1901) demonstrated that the electrical excitability of the cortex cerebri is diminished by the application of isotonic solution of calcium chloride, and that a solution which precipitates calcium—e.g. sodium oxalate—increases the excitability, and may in sufficient concentration induce convulsions. The association of tetany with hypocalcæmic or alkalotic states is well known though it is a common observation, confirmed by the present cases (figs. 2 and 3) that there is no close inverse relationship between the level of the ionized calcium in the blood and the severity of the tetany (Cameron, 1947). Other biochemical changes which may be in part responsible will be reviewed in the other paper.

Noël Paton, Findlay and Watson (1916) investigated the neuromuscular

mechanisms responsible for the tetanic seizures in parathyroidectomized dogs. They found that both central and peripheral mechanisms were involved. They attributed the spasticity, tremors, and jerkings to an effect on the nerve endings, quoting the cross-circulation experiments of MacCallum (1913), but they found no evidence of central neurone involvement. On the other hand they considered that the onset of epileptiform convulsions in advanced cases probably indicated the secondary involvement of the motor cortex. Cerebellar fibres were implicated in advanced cases. Contradictory conclusions were reached by West (1935) who denied involvement of supraspinal centres but confirmed that integrity of the spinal reflex arcs was essential for the development of tonic and clonic manifestations by synthesizing fibrillary muscular contractions due to the action of a "circulatory factor" on the muscles. Greenberg, Boelter and Knopf (1942) state that in rats, tetanic movements of the hind-limbs but not of the fore-limbs are abolished by transection of the cord at the level of the seventh spinal segment. They conclude that activity of supraspinal centres is essential for the development of both the tonic and clonic seizures. The researches of Kugelberg (1946, 1948*a* and *b*) on the Trousseau phenomenon have already been discussed. They indicate that fibrillary twitching and tonic spasm at least can be attributed to hyperirritability of peripheral nerve fibres. He does not discuss the clonic or epileptic manifestations.

These contradictions remain to be resolved. It is probable that the excitability of the whole neuraxis, peripheral nervous system and musculature is increased (probably not symmetrically as shown by Kugelberg). Experiments on animals and *in vitro* show that in hypocalcæmia or hyperventilation states, various nerve structures discharge spontaneously. This has been shown for nerves (Lehmann, 1937), ganglion cells (Bronk, Larrabee, Gaylor and Brink, 1938) and motor end-plates (Kuffler, 1944). Paton, Findlay and Watson (1916) reach the interesting conclusion that "in experimental tetania parathyreopriva there is a certain antagonism between the excitability of the peripheral and that of the central nervous systems, since cases with severe nervous symptoms, e.g. tremors and convulsions, generally present a less degree of excitability of the nerves than those in which the symptoms are little marked or entirely latent," but "in idiopathic tetany in childhood, the electrical excitability bears a closer relationship to the severity of symptoms."

A possible mechanism for the central hyperexcitability, suggested by McQuarrie, Hansen and Ziegler (1941), is that low mineral intake causes increase of tissue water with an associated disturbance in the surface functions of the brain-cell membranes, which permits the building up of abnormal electrical potentials. Barr, MacBryde and Sanders (1938), finding normal levels of total and ionic calcium in the cerebrospinal fluid of their case of hypoparathyroid tetany with papillœdema, suggest a more gross mechanism—namely that differences in concentration of calcium on the two sides of the cerebral membranes might lead to

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accumulation of cerebrospinal fluid. Similar changes in intra-ocular pressure are on record (Lyle, 1948). This explanation would require another mechanism to explain the hyperexcitability of the peripheral nervous system but McQuarrie, Hansen and Ziegler's (1941) theory could readily be made inclusive and in that respect is to be preferred. Further speculation would be premature.

Summary

(1) Two cases of idiopathic hypoparathyroidism are recorded, the syndrome consisting of tetany, trophic ectodermal lesions, skeletal abnormalities and biochemical changes in the blood.

(2) Both cases exhibited hemitetany for several months before this sign became bilateral. There was no evidence of gross cerebral disease.

(3) In Case 1 (a child) additional features were epilepsy, acute hallucinatory psychosis, mental deficiency, a transient choreiform state, separation of cranial sutures, and calcification of the choroid plexus at an unusually early age.

(4) The E.E.G. in Case 1 showed a diffuse slow rhythm which increased to alpha frequency (with occasional delta activity) when the serum calcium was restored to normal. Case 2 (adult) showed mild dysrhythmia, probably within normal limits.

(5) Attention is drawn to headache, excessive muscle weakness, and fatigue as symptoms of incipient tetany.

(6) Tests for latent tetany are reviewed and their mechanisms discussed.

Acknowledgments

I should like to thank Professor Sir John McNee, Dr. D. K. Adams and Dr. L. D. W. Scott for the use of their records and permission to investigate these cases. I am indebted to Dr. S. D. Scott Park and Dr. D. C. Suttie for the radiographs and Dr. S. Renfrew for the E.E.G.s. The biochemical estimations are due to Mr. S. L. Rae and Mr. T. G. Pirie.

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ELECTRICAL CORRELATES OF THE SPINAL FLEXOR REFLEX[1]

BY

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SHERRINGTON (1903) has found that nocuous sensory stimulation of a limb of a decerebrate or spinal mammal can evoke its reflex withdrawal. This is a complex and organized movement, involving successive flexion of foot, leg, thigh which takes place in an appreciable length of time. Artificial stimulation of a cutaneous nerve by means of single electric shocks evokes only a brief twitch of flexor muscles if the stimulus is weak, but if the strength of the stimulus is increased, the reflex discharge and the contraction of the flexor muscles is greatly prolonged. This prolongation of the reflex discharge following strong electrical stimuli is called "after-discharge" (Sherrington, 1921). Since the afferent discharge from cutaneous receptors can outlast the duration of the applied stimulus (Adrian, 1926, 1928—p. 72), the prolonged reflex discharge following sensory stimulation could conceivably be attributed to the long duration of the afferent trains of impulses. The electrical stimuli which give rise to after-discharge, however, only set up a single volley in the stimulated nerves (Sherrington, 1921). This after-discharge must then be the consequence of long-lasting excitatory process taking place in the central nervous system. Creed, Denny-Brown, Eccles, Liddell and Sherrington (1932—p. 42) and Forbes (1922) assume that this excitatory process is due to temporal dispersion of the afferent impulses in the spinal cord, partly due to difference of conduction velocity in different fibres and partly to different synaptic delays.

If the movement resulting from electrical stimulation of a cutaneous nerve is observed in a limb with intact innervation, it can be seen that, while weak stimuli do not evoke organized movements, but only short twitches which are hardly appreciable under the skin, strong stimuli are followed by complete withdrawal of the limb, which closely resembles both in the pattern of organization of the muscles involved and in the duration of the contraction, the movement induced by adequate sensory stimuli. In a recent related experimental study (Brooks and Fuortes,

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1952) we found in confirmation of previous results (Barron and Matthews, 1938) that the electrical correlates of the flexor reflex, as led off from ventral roots, naturally divides into two groups. The first has a minimal central delay of about 3 msecs. and a duration of approximately 5–10 msecs. The second is evoked only by rather strong stimuli and follows the first with or without delay. The duration of this second component is variable and depends upon the intensity of the stimulus, but it always persists for a considerable fraction of a second. When recorded with suitable technique and direct current amplification, both groups of discharges are seen to arise from slow, non-propagated negative waves indicating depolarization of the motoneurones (Barron and Matthews' ventral root potential). The former group clearly corresponds to Lloyd's (1943) so-called plurisynaptic reflex, while the latter can be identified with the most conspicuous phase of Barron and Matthews' (1938) ventral root potential (*see* their fig. 14F). The temporal features of these reflex waves indicate that the first group is the electrical correlate of Sherrington's flexor reflex twitch and the second corresponds to the after-discharge (fig. 1).

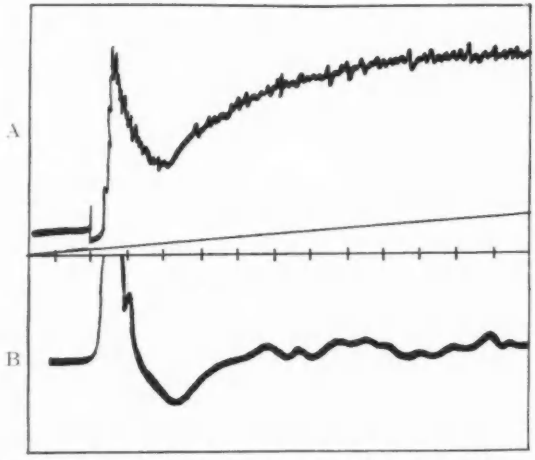

FIG. 1.—A comparison of ventral root potential and muscle action potential. A, Electrical correlates of reflex as picked up from ventral roots. B, Reflexly induced muscle action potentials (Eccles and Sherrington, 1931). 10 msec.

If now the reflex movements evoked by sensory or by electrical stimulation are observed while their electrical correlates, led off from a ventral root, are simultaneously fed into a cathode ray tube and a loud speaker, it is immediately apparent that the withdrawal of the limb corresponds to the second wave, i.e. to the after-discharge.

In decerebrate or spinal preparations, following recovery from initial anæsthetization with ether, electrical stimulation of gradually increasing strength is followed by withdrawal of the limb only when the stimulus

becomes strong enough to give rise to the electrical signs of after-discharge (fig. 2). When after-discharge is present, it coincides in time with the movement.

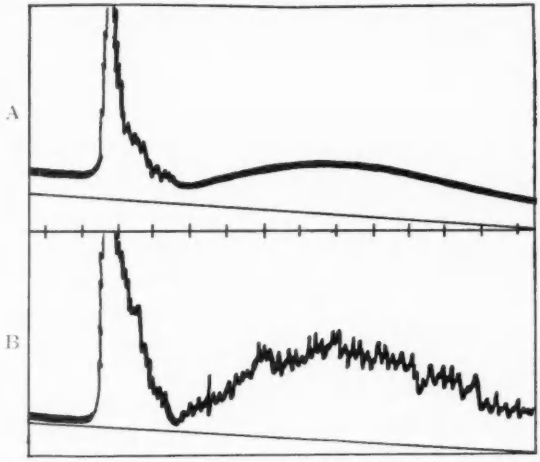

FIG. 2.—Ventral root potential in a decerebrate cat induced by single shock stimulation of an ipsilateral cutaneous nerve. A, Weak stimulus not followed by after-discharge or movement. B, Stronger stimulus resulting in withdrawal of the limb. 10 msec. intervals.

In preparations anæsthetized with barbiturates (nembutal 30–45 mg./kg.), strong sensory stimulation only gives rise to barely perceptible reflex movement. The electrical correlates of the reflex activity are also minimal. Electrical stimulation, in contrast, is generally followed by very clear asynchronous electrical waves of short duration which are propagated to the flexor muscles. No after-discharge ever appears in these conditions of anæsthesia. Correspondingly, the only movement which can be perceived in the stimulated limb is an inconspicuous twitch of short duration, and withdrawal never takes place.

The conclusion which we derive from these observations is that the first group of reflex waves is expression of a very simple and unorganized reflex property of the spinal cord which becomes experimentally apparent when the excitatory stimulus is a synchronous volley, while the after-discharge is the correlate of elaborated reflex activity capable of giving rise to organized and purposeful movements.

The physiological significance of the after-discharge is evident: it expresses the fact that the central nervous system has elaborated a pattern of motor activity which will cause the limb to withdraw from a nocuous stimulus. How the nocuous character of the stimulus is recognized does not appear from our results. It might be a matter of number of fibres excited, or a matter of particular types of fibres stimulated by stronger stimuli. Selective excitation of fibres of low excitability con-

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ceivably might give an answer to this question. On the other hand, the functional importance of the earlier and simpler reflex twitch is not clear since the movement resulting from it would be insufficient for the removal of the limb from contact with a damaging agent. The sharp separation of the electrical correlates of the first group of reflex waves and of the after-discharge as well as their different sensitivity to anæsthesia indicate that these waves have an independent origin and the mechanism giving rise to the first response is not the fundamental mechanism underlying the development of the late reaction.

Granted that Barron and Matthews' late phase of the ventral root potential is the electrical correlate of the after-discharge, it seems pertinent to call attention to the fact that these authors suggested that this late wave is due to activity reaching the motoneurones via interneurones, while the preceding discharge was considered by them to be evoked by activity reaching the motoneurones directly from afferent terminals. In contrast with this latter concept the currently accepted conclusion is that all discharge following excitation of cutaneous nerves is dependent upon internuncial activity (Lloyd, 1949). This conclusion is based on the finding that monosynaptic reflexes can have a latency of 0·6 to 0·9 msec. (Lorente de Nó, 1935, 1938; Renshaw, 1940) and on the assumption that the latency of a single synapse cannot vary beyond these limits. Since this latter assumption is valid only in limited experimental conditions the evidence cannot be considered final as yet. Indeed, Hodgkin (1948) has shown that wide variations of response-time are found in the initiation of excitation of structures resembling in their behaviour the neurons of the spinal cord. However, further experimentation using recording from single motoneurons will be required before it is possible to decide whether the early group of discharges evoked by cutaneous nerve stimulation is late monosynaptic discharge or an interneurone-mediated reflex containing fewer synapses and shorter elements than the pathways giving the after-discharge which is clearly mediated by interneurones.

The suggestions of Barron and Matthews and the more recently acquired facts concerning the localized action and brief duration of the monosynaptic reflex do provide a basis for understanding the different features of reflex and after-discharge. This study of the electrical correlates of reflex action supports the assumption that internuncial activity can bring about elaboration of the afferent message resulting in purposeful movement, while such complex integration does not take place when motoneurones only are activated. This conclusion seems reasonable and acceptable in the frame of present knowledge of spinal reflex activity.

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A NOTE ON CORTICAL CYTO-ARCHITECTONICS

BY

W. E. LE GROS CLARK

Over the last fifty years, several neurological anatomists who have interested themselves in the cerebral cortex have sought to construct maps of cortical areas which are stated to be distinguishable by structural differences. In some cases these architectonic charts have been elaborated to a degree of complexity which certainly arouses admiration for the industry of the cartographers, even if at the same time they induce an attitude of some scepticism. But it is only recently, when the possible relationship of cortical architectonics to functional localization has appeared to assume an importance in physiological experimentation, clinical diagnosis, and the surgical treatment of certain psychological disorders, that the parcellation of the cerebral cortex by anatomists has begun to be subjected to careful and critical scrutiny. Not unexpectedly, one of the results of this scrutiny has been to correct misconceptions and errors of emphasis which have almost inevitably arisen in attempts to interpret the significance of structural differentiation in the cortex, and also to question the validity of the anatomical criteria on which many of the cortical areas have been defined.

During the last few years, there have appeared from the University of Illinois a series of monographs by Bonin, Bailey and others on the cortical areas of the brain in several primates, *Galago* (Bonin, 1945), the marmoset (Peden and Bonin, 1947), the macaque monkey (Bonin and Bailey, 1947), the chimpanzee (Bailey, Bonin and McCulloch, 1950) and Man (Bailey and Bonin, 1951). The last publication, entitled "The Isocortex of Man,"[1] suggests that most of the smaller cortical subdivisions defined by previous workers in the human brain are not based on anatomical criteria which are objectively demonstrable, that, in fact, they are little more than the products of imagination. If this is so, the greatest caution is demanded in attempting to relate any of the classical architectonic charts of the cortex to physiological or clinical studies.

That the cerebral cortex of man and other mammals is not of uniform structure has been well established for over a hundred years. That the differences may be so marked and so abrupt as to permit the spatial demarcation of adjacent areas, in some cases at least, is also quite well recognized. For example, the cellular character of the dentate gyrus is

[1] Percival Bailey and Gerhardt von Bonin. Univ. Illinois Press, 1951, Pp. X, 301.

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in sharp contrast with that of the adjacent cortex of the hippocampus. The latter can be quite easily distinguished from the subicular cortex, and this again from the neighbouring neopallial cortex. The visual cortex in most primates, also, has such a characteristic structure that its limits can be defined in sections even with the naked eye. The contrast between the precentral and postcentral cortex of the primate brain is likewise perfectly evident to anyone who takes the trouble to examine appropriate sections. Such instances of structural differentiation, sufficiently distinct to justify the delineation of the boundaries between the corresponding areas in a cortical chart, are not illusions; they have been confirmed by all those who have made a special study of the cerebral cortex, and they can be so readily verified by anyone at any time that their existence is hardly likely to be denied. But difficulties have arisen ever since the recognition of *some* degree of cortical differentiation led anatomists to extend the conception of specific cortical areas from a few main regions (where they are apparent enough) to every part of the cortex. It was perhaps almost inevitable that some ardent workers should strive to parcel out the whole cortex into a greater and greater number of smaller and smaller areas, and that in order to do so they should come to rely on histological differences of such a subtle nature as to raise serious doubts about their objectivity.

The first systematic attempts to map cortical areas on the basis of histological differences were reported in 1905 by A. W. Campbell and K. Brodmann. These pioneers were not only concerned with the human brain; they made comparative studies of the cerebral cortex of lower mammals and attempted to homologize the different structural areas and determine their relative development in different species. These early studies, at least so far as lower mammals are concerned, have been shown by subsequent workers to be reasonably accurate in regard to the main areas. For example, apart from rather trivial differences in the relative extent of certain of these areas (presumably an expression of individual or specific variations), Peden and Bonin's chart of the marmoset brain almost duplicates that of Brodmann. Again, if Brodmann's cortical map of the monkey *Cercopithecus* is compared with that charted by Bonin and Bailey for *Macaca*, it is interesting to find how closely they agree. Such differences as do occur are mostly explicable as generic variations. On the lateral aspect of the monkey hemisphere, Brodmann distinguished seventeen separate areas, and Bonin and Bailey only two less. On the medial aspect, the corresponding figures are twenty and seventeen. Differences are certainly found in the parcellation of the frontal and temporal lobes, but the corresponding main areas coincide quite closely, and moreover show approximately similar topographical relationships to the principal sulci. Brodmann's chart is a black-and-white diagram in which the several cortical areas are indicated by distinctive markings, dots of various sizes, lines and cross-hatchings, circles, etc.; that of Bonin and Bailey is displayed in gay colours. One of the

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advantages of the latter is that transitional zones which occur between certain of the areas (and which are specifically noted by Brodmann in his text) are more easily represented in a chart. As the result of their highly critical studies of cortical architectonics in the spider monkey and the macaque monkey, Lashley and Clark were also able to recognize by consistent structural features some of the main areas previously described, but they take the view that the further subdivision of these regions has been based on variable characters which probably have no functional significance. In particular, these authors have emphasized the great individual variability in the relative extent of some of the structural areas, a variability which does not seem to have been fully realized by their predecessors.

Mention has been made above of transitional zones between adjacent areas of the cortex. In some cases these are non-existent, or almost so. Thus, the boundary of the visual cortex (area striata) is quite sharp in the brains of most higher primates. The boundary between the precentral and postcentral cortex is also relatively abrupt almost everywhere, though a close inspection of microscopic sections reveals a very narrow transitional band to which attention was called by Brodmann and which he referred to as a "Mischzone." On the other hand, other areas, particularly those near the frontal pole of the hemisphere, are said to grade almost imperceptibly into each other. It is mainly in regard to areas of this type, of course, that dispute has arisen on (1) the validity of attempting to separate them at all, or (2) the position of the approximate line of demarcation between them. Brodmann, indeed, well recognized these difficulties, and he was careful to warn his readers that, because of structural intergradation, his subdivisions of the frontal pole in the macaque brain were to some extent arbitrary ("etwas willkürlich").[1] But even if two adjacent areas grade into each other, this does not necessarily mean that they are not distinguishable structurally. The "motor" area, with its characteristic concentrations of large Betz cells (at least in its upper part), is not separated from the "premotor" area by any sharp line of demarcation; yet some degree of structural differentiation between these two areas has been noted by all those who have made histological studies of this region of the cortex. Again, the fact that outliers of typical Betz cells may occasionally be seen here and there in the postcentral cortex does not lessen the fact that the latter is rather sharply contrasted in its cyto-architectonic features with the precentral cortex. A pertinent analogy may here be made with structural differentiation in the alimentary tract. It is well recognized that the gastric mucosa can be subdivided into at least three zones each of which is characterized by its glandular structure; yet there is no well-marked and abrupt

[1] Bailey and Bonin, it may here be noted, are perhaps a little unkind to Brodmann in translating "willkürlich" as "gratuitous," for this word has come in the English language to acquire a rather unpleasant derogatory meaning which they probably do not intend.

demarcation between them. Again, the fact that outliers of gastric mucosa may occasionally occur as small patches in the lower end of the œsophagus does not alter the fact that the œsophageal mucosa is very different indeed from the gastric both in structure and function, and that (in this case) the line of demarcation is quite sharp. It is nevertheless true that some students have tended to accept areas outlined on cortical charts as sharply defined entities with rigid and invariable boundaries, even though such an implication was not necessarily intended by the cartographer. This is an obvious danger inherent in any attempt to reproduce cortical complexities in what is clearly intended to be a diagrammatic form, even when the diagram is accompanied by adequate qualifications in the text, and it is perhaps a contingency for which no author can properly be held responsible. All this is not to say, however, that some anatomists have not overstepped what might be termed a legitimate "diagrammatic licence" by multiplying subdivisions of the cortex and outlining them with an apparent finality which almost forces upon the unwary reader the idea that they really *are* clear-cut and easily distinguishable by their structure. This does not apply so much to the main cortical areas represented, for example, in the monkey's brain by Brodmann and Bailey and Bonin. But it certainly does apply to minor subdivisions. In this connexion, it is important to draw attention to the marked distortion of the histological appearance of the cortex which is produced by the folding of the surface of the brain. Over the summits of convolutions, for example, the superficial laminæ tend to be relatively thinner and the cells more spaced out, while in the depths of sulci the laminæ are compressed and the cells, being more tightly packed, may assume different shapes. Where adjacent cortical areas are only to be distinguished (if at all) by minor differences in cyto-architecture, these disturbing effects of cortical folding introduce a complicating factor which renders their accurate differentiation almost impossible. If, further, account is taken of the fact that the convolutions themselves differ greatly in their shape and that the appearance of the cortex also varies enormously according to the obliquity of section, it will be realized that the attempt to subdivide small areas of the cortex on the basis of slight differences in the relative widths of the laminæ or in the shapes of the constituent cells is hazardous in the extreme. Indeed, so far as the frontal lobe of the monkey's brain is concerned, it is perhaps hardly legitimate to recognize more than three main architectonic areas on the lateral surface—the "motor" area (characterized by concentrations of Betz cells), the agranular "premotor" area (not sharply separated from the "motor" area), and the granular frontal area (usually demarcated from the "premotor" area throughout much of its extent by the arcuate sulcus). It is probable, no doubt, that each of these main areas shows some regional variations in cyto-architecture, but it may be questioned whether such variations are sufficiently marked or consistent to justify delimitation on a chart. It also needs to be recognized that the main

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areas themselves show pronounced individual variations in their relative extent.

If, as we surmise, some cartographers have been misled by local distortions of cyto-architecture due to foldings of the cortex (and have thus made minor subdivisions of main cortical areas which have no practical significance), it is perhaps to be expected that in the more richly convoluted brains there would be a greater measure of disagreement in charts constructed by different anatomists. Certainly it is in regard to the human brain that there is least agreement. We have already noted that there seems to be a reasonable consistency in the delineation of some of the main areas of the cortex of lower primates as shown in charts drawn up independently by different authorities. Even the chart of the chimpanzee brain constructed by Bailey, Bonin and McCulloch, which is a gay patchwork of many contrasting colours, reproduces the main architectonic features previously mapped in the ape's brain by Mauss. But it is when we come to Bailey and Bonin's chart of the human brain that discrepancies really become serious. For, in contrast with Brodmann's variegated map, in their chart a considerable extent of what are usually termed the "association areas" is represented in a uniform pink colour. It is true that in their description the authors do note certain local differences in their pink areas, but they regard them as too slight and uncertain to justify separate representation. The explanation for this discrepancy is probably complex. Apart from the possible misinterpretation of local distortions in laminar architecture due to purely mechanical factors, Brodmann may have been imbued with the idea (by no means necessarily true) that the human cerebral cortex ought to show much greater structural differentiation than lower primates, and thus allowed himself to see local differences which were really too vague and variable to be defined by any objective criterion. Unfortunately he died, at a comparatively young age, before he published a detailed account of the evidence on which his chart of the human brain was based. Had he been able to publish this account, it is probable that he would have emphasized its strictly diagrammatic nature (though even this might not have prevented the careless reader from accepting it as an accurate representation of reality). But if Brodmann's representations of some of his minor cortical areas are no more than schematic approximations (and the careful studies of Bailey and Bonin certainly seem to indicate that this is so), there can surely be no justification at all for the elaborate parcellations drawn up by what may be termed the Vogt school. These complicated charts have been suspect for some time, and Bailey and Bonin are rightly outspoken in condemning them. It is little wonder that such extremists have led the more critical reader to doubt whether even the main cortical areas have any real existence, and their enthusiastic essays may perhaps be dismissed now from any further consideration. Bailey and Bonin recognize by structural and topographical criteria that the human cerebral cortex can be subdivided into about

twenty main areas, and this is perhaps as far as most neurologists will be inclined to accept the subdivision at present. This is not to say, however, that further subdivision on a structural basis may not prove valid with objective methods of estimating differences. The recent work of Dr. Elizabeth Beck on the cyto-architecture of the orbital surface of the frontal lobe is an advance on the more cursory method of delimiting areas by direct inspection of microscopic sections of a single brain, for she took photo-micrographs of every hundredth section in order to facilitate comparison, only took note of what she terms "striking alterations" in the laminar pattern, and only recognized those areas which could be identified consistently in nine hemispheres. But even this careful study is not likely to satisfy the critical reader who would maintain that reliance can only be placed on differences which can be expressed quantitatively. Incidentally, we may note that Bailey and Bonin themselves have ultimately to rely on differences in structure which they can only express in general terms. For example, in describing the characteristics of one type of cortex in the human brain (p. 65), they state "There follows a third layer, *somewhat thicker* than the second one, which contains a *sparse* population of *not very* large cells . . . *rather irregularly* strewn about . . . There follows a thin zone *almost devoid* of cells, except for a few scattered *small or medium-sized* pyramidal cells. . . ." All the words which we have italicized in this extract are open to criticism since they are obviously based on a subjective assessment. No doubt this is inevitable in preliminary studies of a structure so extremely complicated as the cerebral cortex, but so long as such differences are not expressed in quantitative terms, so long must there remain some doubt on the validity of minor parcellations.

The question arises whether the main architectonic areas of the cerebral cortex are also to be distinguished by differential fibre connexions as well as by structural differences. To some extent this certainly is the case, as may most readily be demonstrated by reference to the monkey's brain (in which the problem has been studied experimentally). The striate area, for example, is the projection area of the lateral geniculate nucleus; the postcentral area receives afferent fibres from the posterior ventral nucleus of the thalamus (which, in turn, receives the terminals of the sensory tracts of the brain-stem and spinal cord); the "motor" area receives fibres from the intermediate (lateral) ventral nucleus (which, in turn, is the terminal station of fibres from the cerebellum); and the granular cortex of the frontal pole is the receptor area for the dorsomedial thalamic nucleus. Indeed, it is possible to subdivide the cortex of the monkey's brain into at least twelve different areas each of which is distinguished by its specific relationship to one or other of the thalamic nuclei. It is also a matter of considerable interest that these areas do, in fact, show a reasonably close coincidence with the main architectonic areas as defined by Brodmann, Bonin and Bailey, and others. It is this relationship, of course, which has given rise to the supposition that even

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the minor architectonic areas which have been described may also be characterized by differential types of fibre connexion. So far, however, there is little direct anatomical evidence for this, though it is an interesting fact that there is rather a precise localization in the projection of each part of a single thalamic nucleus to specific and circumscribed regions of the corresponding main architectonic area to which it sends its axons. But it is necessary to point out that even the differential connexions of the main areas may not be circumscribed with *absolute* exactness. For example, all the anatomical evidence appears to indicate that in the monkey the boundaries of the striate area of the cortex are coterminous with the boundaries of the projection area of the lateral geniculate nucleus. But with the available anatomical techniques the possibility cannot be discounted that occasional stray fibres of the optic radiation encroach on the immediately surrounding zone of the cortex (though even if this does occur it is perhaps of very little significance functionally). Again, there may be a certain degree of overlap in the termination in the ventral thalamic nuclei of fillet fibres and fibres from the cerebellum, and a corresponding overlap in the thalamo-cortical impulses reaching the precentral and postcentral convolutions. But the anatomical evidence seems fairly clear that if such an overlap does occur it is probably inconsiderable. Thus, while it is perhaps somewhat naïve to suppose that in a complex biological system such as that represented by the cerebral cortex anything is clear-cut with mathematical precision, there obviously is a parcellation of some sort based on differential fibre connexions, and this parcellation does broadly coincide with main architectonic areas.

Bailey and Bonin point out that it is now well established that certain structural peculiarities of the cerebral cortex are co-extensive with areas of special functions. The striate area, for example, has the special function of receiving spatially organized impulses from the retina, and the agranular area in front of the central sulcus subserves motor functions in the normal brain. Particularly instructive in this connexion is a comparison of Brodmann's charts of the cortex in the rabbit and monkey with those of Adrian depicting the outline of the general sensory cortex, for here the coincidence between the structural areas and those responding by electrical activity to peripheral stimulation is remarkably close. But this occasional correlation of functional distinctions with structural distinctions in the cerebral cortex has led, not unnaturally, to the surmise that the less well defined subsidiary areas mapped out on cortical charts may also be characterized by some degree of functional specificity. It is this line of thought, no doubt, which has recently led to a critical reconsideration of the factual basis of cortical architectonics, as well as to a more careful evaluation of the significance of functional differences apparently exposed by physiological experimentation. Bailey and Bonin go so far as to affirm that "the purely tentative results of Brodmann ... have been accepted by physiologists as of divine authority and a vast superstructure has been built on this shaky foundation which is

now being extended to the human brain by the neurosurgeons." This statement is evidently to be regarded as a rhetorical hyperbole (for it otherwise implies rather a serious reflection on the critical faculties of physiologists in general), but it clearly contains an important element of truth. There has perhaps been a tendency for some neurologists to focus attention on differences in cortical structure (which in some cases may be very slight) rather than on the all-pervading similarity of the cortex as a whole. This, again, has led to a tendency to over-emphasize the functional differences where these are known to exist. The statement of Hughlings Jackson, in reference to the central nervous system, that "difference of structure of necessity implies difference in function" is no doubt broadly true, but the converse is also true. It is important, moreover, to recognize that such structural differences as do occur between cortical areas are of a quantitative rather than a qualitative nature and that, in general, even these quantitative differences are slight. Thus the laminar characteristics of the visual cortex are not in themselves specifically dependent on *visual* functions—they seem to be mainly related to the fact that the afferent fibres which this area receives from lower levels are particularly numerous and closely packed.

Lastly, it seems desirable to stress that, when the statement is made that one cortical area has certain functional activities which distinguish it from another area, it is not intended to imply that these functions can be precisely defined in psychological terms. The striate area, as the receptor area for retinal impulses, is essential in the normal human brain for visual perception, but this statement by no means defines the totality of its functions as a component of the very complex mechanism on which visual perception depends. Similarly, stimulation and ablation experiments, as well as clinical observations, lead to the inference that the "motor" cortex in the normal brain serves *some* function in the control of voluntary movement, but again it is not yet possible to define this function in the terms of the Oxford Dictionary as "the mode of action by which it fulfils its purpose." It seems possible, indeed, that there may have been a misunderstanding of the term "function," as it has been used by different writers, in some of the recent discussions on cortical localization. Bailey and Bonin very rightly remark that, though we understand fairly well the functional organization of input signals into the cortex and also know that output signals normally emerge from the "motor" area, "that is, however, certainly not the whole story."

Considering the complexities of cortical anatomy and physiology, it may be doubted whether we ever shall know the whole story. But in our attempts to know even a part of it, Bailey and Bonin have made a notable contribution by their critical and careful studies of cortical architectonics. Above all, their work has emphasized—and it will be generally agreed that the emphasis is timely—that Brodmann's charts (and also their own, presumably) are to be regarded as no more than schemata. Further, while the main areas indicated in them may be

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accepted as broadly correct in extent and boundaries—with a due recognition of their individual variability—the validity of some of the minor areas (to say the very least) is not beyond doubt. Finally, neurologists should continue to regard with the greatest suspicion the incredibly complicated "crazy-pavement" maps of cortical areas which have from time to time been elaborated by the Vogt school since Campbell's and Brodmann's original studies were first published.

Notices of Recent Publications

The Electrical Activity of the Nervous System. A Textbook for Students. By Mary A. B. Brazier. 1950. London: Pitman & Sons.

This book is written in a clear straightforward manner and is well illustrated by diagrams and experimental records. It is about as advanced as one of the larger physiological textbooks.

Clarity is achieved in this highly analytical subject chiefly by confining the treatment to a statement of observation and of the opinions of authorities. In this sense only is the book "authoritative."

The "student" for whom it is written is thus presented with clear facts and ready-made opinions in a wide field, but he is never invited to think for himself nor is the material presented in such a way as to enable him easily to do so. For many of the views quoted appear too obscure to be intelligible and too eminent to be omitted.

It is always hard in a book of this kind to prevent errors of oversight from creeping in, such as the statement (p. 32) that in the subnormal period conduction velocity is unimpaired, while on the next page it is said to be slowed. Or the remarkable result attributed to Hartline (p. 151) that the eye of *Limulus* is equally excitable to every wavelength of the electromagnetic spectrum. The chapter on the Visual System, however, will need revision.

The most surprising thing here is that the author appears simply unaware of the difference in the impulse pattern to be expected from a nerve which leads directly from a sense organ such as a muscle spindle or a photoreceptor cell in the eye of *Limulus*, and the vertebrate optic nerve which has the whole complexity of the retinal layers interposed between the primary response and the record. Thus having described only the vertebrate optic nerve, she gives a record (fig. 67) from a structure simply called "optic nerve" which in fact is from *Limulus*. The optic nerve of the vertebrate is described as "the only *nerve from a sense organ* giving an off-response," and this off-response is incorrectly stated to have been found by Hartline in *Limulus* (where it does not occur). As Hartline's analyses and writings are models of clarity, this confusion is surprising.

It should be a timely inspiration for the student of science to see how light has been thrown upon the problems he studies by contributions from every race of free and highly civilized man. Mary Brazier has adopted a more nationalistic approach.

When Davis, Forbes *et al.* confirmed the work of Kato, published two years previously, invalidating Lucas' and Adrian's method of measuring the size of the nerve impulse, they characteristically gave full priority to the Japanese work, though much of their own had been done independently. For Dr. Brazier, however, it is the American experiments which are primary (p. 18) and she merely adds "Kato's work gave similar results."

This example, unfortunately, is not unique. "Forward conduction in the reflex arc," whatever that may mean, "was recognized by William James"—fifty years after Bell and Magendie had enunciated the law which bears their names.

The massive structure of evidence by which Dale and his colleagues have established the role of acetylcholine at nerve endings is placed before Dr. Brazier's students in

this single sentence " . . . and the discovery by Dale that acetylcholine may mimic parasympathetic action led to the well-known work of Cannon and his school . . ." (p. 10).

It is in Helmholtz, however, that she reaches her apogee of disparagement. By contrast John Fulton has written "One of the greatest thinkers of all time . . . (he) became at the age of 28 a professor of physiology at Königsberg. . . . His phenomenal powers of abstract thinking had not been approached in any field of thought since the days of Newton. . . . One cannot enumerate all of Helmholtz's contributions to physiology; everything he touched, except psychology, was as if by magic turned to gold." Mary Brazier simply remarks (p. 19): "He was a Prussian army surgeon with interests far wider than his duties, who invented a 'myograph' by which he measured the velocity of the nerve impulse in frogs."

W. A. H. R.

Functional Neuro-anatomy. By A. R. Buchanan. 2nd Edition. Pp. 323 with 273 illustrations. London: Henry Kimpton. Price 52s. 6d.

This edition of a popular students' book has been improved by the addition of an atlas of the brain-stem consisting of plates of 30 horizontal sections of the brain-stem from the decussation of the pyramids to the thalamic level of the massa intermedia, and 6 coronal sections through the anterior part of the basal ganglia. In these plates one-half is shown as stained for myelin while the other is a line drawing outlining the more important structures. It is unfortunate that the two sides do not correspond exactly; the drawing is never a mirror image of the photograph and often appears to have been taken from a section at a different level, so that it is often difficult to make out which appearances in the photograph correspond to nuclei or tracts named in the drawing. Sometimes a structure appears in the diagram of one plate and in the photograph of the next one, e.g. the external geniculate body in figs. 250 and 252. We should also have liked coronal sections through the posterior two-thirds of the thalamus, which is most often examined by sectioning in this plane. In spite of these faults the atlas is a valuable addition, and perhaps the best part of the book. The text itself is a statement of the anatomy of the nervous system in simplified form, illustrated by fragments of physiology, pathology and clinical neurology. This method of presentation is no doubt appreciated by the junior student, who seems to need the interest supplied by clinical syndromes to relieve the dullness of anatomical detail; but it makes the book of relatively little use to the senior student and neurologist, who are already supplied with much more complete textbooks of the anatomy and physiology of the nervous system.

J. G. G.

Genetic Neurology. Problems of the Development, Growth and Regeneration of the Nervous System and its Functions. Edited by Paul Weiss. The University of Chicago Press. Pp. 239. Price 37s. 6d.

In March 1949 an International Congress was held at the University of Chicago under the sponsorship of the International Union of Biological Sciences to discuss certain problems grouped under the general heading of Genetic Neurology. This

term was intended to connote not only problems of heredity and development but also those of regeneration and restitution after injury. In the event the intimate structure of the neuron, as "viewed through atomic spectacles" (Schmitt), was also discussed. The point of view of the Congress was essentially histological and in spite of the subtitle little was said about the function of the neuron. After the congress those taking part were asked to contribute short essays on their own subjects, and these essays, with an introduction by Dr. Paul Weiss, who acted as Chairman, form the present volume. This introduction is a valuable article covering in a general way a large part of the field which is dealt with in more detail by the other contributors.

The outcome is a book which, though small, is full of interest and stimulus. Many of the articles deal with relatively new work, for example that resulting from the employment of the new techniques of election microscopy, X-ray diffraction and spectroscopic studies using rays of limited wavelength. On the whole this work tends to confirm old views rather than to add fresh and revolutionary knowledge. In other articles some of those who have spent many years in work on the neuron, such as C. C. Speidel, R. W. Gerard and J. Boeke, have given up-to-date surveys of their results. The article by Professor Boeke is especially interesting and provocative, challenging both current cellular theories and the conception of the neuron as a separate cell unit. If we understand him correctly the parts of the nerve cell which, in his view, are continuous to the end organ are the neurofibrils and their surrounding neuroplasma. These "lie in the protoplasm of the conducting cell" (Schwann cell, end plate, connective tissue cell of the muscle spindle, etc.) and the two protoplasms appear to fuse. This article raises again the old difficulty of the relation of myelin and sheath of Schwann to the axon, and the old question whether axonal outgrowths may be naked as Cajal held, or are always covered by sheath cells, as in Nageotte's view. It seems difficult to reconcile Boeke's views with the theories on the behaviour of growing axons which are summarized in other articles of the present series. Thus W. H. Lewis from motion picture studies considers the axon to be composed of a superficial gel layer and a less viscous endoplasm; "the gel layer always exerts contractile tension; all the movements exhibited by the neurons . . . are due to local variations of the contractile tension of the superficial gel layers of the cells." Paul Weiss found that axoplasm becomes dammed up behind a constricted region, and J. Z. Young conceives of the nerve fibre as "a very long thin column of viscous liquid enclosed in a wall that resists stretch, has some elasticity and is permeable to some of its liquid contents."

While most of the book deals with the constitution of the neuron several interesting chapters discuss embryology, especially from the experimental side, and the relationship of maturation of neurons to reflexes and early behaviour. The latter, although long a matter of interest, still remains largely hypothetical, different workers getting widely different results. Indeed the book as a whole, while giving us a glimpse of the promised land, shows how wide a river of ignorance and uncertainty still separates us from it.

Although the book makes no pretence to be a work of reference, the absence of an index detracts from its value. Many of the articles also show how American of the Middle West is becoming divorced from English as used in this country; there are several neologisms, such as "aneurogenic" (for nerveless), "relatedness" (for relationship) and many words are used in senses different from those current on this side of the Atlantic, e.g. "specified" appears to mean "differentiated." In many articles, too, the American love for abstract nouns obscures the author's meaning. Are we nearing the time when a course in "Scientific American" will be an essential part of the curriculum in our Universities?

J. G. G.

XUM

Principles of Neurology in the Light of History and Their Present Use. By WALTHER RIESE. Nervous and Mental Diseases Monographs. New York, 1950. Pp. 177. Price in U.K. 48s.

Those who, during the past decade, have read the thoughtful papers of the author of the present monograph, as they have appeared from time to time in the *Journal of Nervous and Mental Diseases* and in the *Bulletin of the History of Medicine*, will welcome this synthesis of his neurological thought. Many and brilliant are the workers who have added to neurological knowledge, anatomical, physiological, pathological and clinical, during the past eighty or ninety years, but too few have been found ready or able to develop a worthy corpus of neurological principles, from which alone can the full harvest of our knowledge be gathered.

Dr. Reiss has acknowledged his debt to three great masters of theoretical neurology, Hughlings Jackson, von Monakow and Kurt Goldstein, and his monograph is an impressive critical synthesis of their teachings, informed by the author's own philosophical and erudite mind. Von Monakow's contribution is perhaps the least well known of the three, largely because of its appearance just at the outbreak of the first world war, but partly also because of the difficulty of his German and from the recondite quality of his thought, yet he was, following Jackson, one of the first writers to draw the clear distinction between symptoms and functions, and to point to the common error of confusing under the term "localization," the three categories of structure, normal function and that disorder of function we name the symptom.

Dr. Riese is an informed student of Jackson's teachings, one of the few who write with insight of them, and his critical assessment of them is valuable. Thus he amplifies the notion of "resistance" which Jackson but lightly sketched and places it in relation to "inhibition" as to its nature and its purpose. For Jackson's hierarchy he substitutes the notion of the "mobile hierarchy" of levels, by which the dominant element in the levels is to be regarded as not fixed but as varying, or alternating.

He amplifies the notion of "release symptoms" by adding that which Goldstein speaks of as the "catastrophic reaction," in which resistance to abnormal impulses being broken down a disastrous reaction takes place; of such, hemiballismus may be cited as an example.

Von Monakow's diaschisis receives its first really extensive exegesis in the English language.

Many sage aphorisms and pronouncements are to be found in these ripe pages.

Thus, "Though we learn from *Cybernetics* that machines and technical devices can now be constructed which display purposeful 'behaviour,' we should not overlook the fact that the organism will always differ from the most ingeniously constructed machine by the fact that it has its teleological principle in itself, whereas the machine serves and reaches the purpose imparted to it by its builder. That is why the organism, a self-regulated whole, can grow, reproduce and repair itself. No machine will ever be constructed able to perform these basic functions of life. In the final analysis all we might ever learn from machines, imposing as they are, we owe to ourselves as their creators. In fact, the adherent of Cybernetics, using the machine as a model of organic processes, falls back on himself as on his own original."

Riese might well have added that the machine does not begin to work until the last rivet and connexion are in place, and may cease to work when the first of either falls out. The living organism begins to work out its purpose from the moment of conception and strives to accomplish it until final dissolution.

It would be impossible to do justice to this monograph in a short review. Dr. Riese has placed his colleagues under a great debt, and it is to be hoped that his work will prove a potent stimulus to neurological thinking.

It remains to add that it is not always easy reading, for in places the idiom is not really English. This is a minor defect in an exhilarating book. F. M. R. W.